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ADVERSE DRUG REACTIONS: ARE SAFEGUARDS ADEQUATE FOR THE ELDERLY?

HEARING

BEFORE THE

SPECIAL COMMITTEE ON AGING
UNITED STATES SENATE

ONE HUNDREDTH CONGRESS

SECOND SESSION

WASHINGTON, DC

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ADVERSE DRUG REACTIONS: ARE SAFEGUARDS ADEQUATE FOR THE ELDERLY?

FRIDAY, MARCH 25, 1988

U.S. SENATE,
SPECIAL COMMITTEE ON AGING,
Washington, DC.

The committee met, pursuant to notice, at 9:30 a.m., in room 628, Dirksen Senate Office Building, Hon. John Melcher (chairman of the committee) presiding.

Present: Senators Melcher, Shelby, Heinz, Domenici, Burdick, Durenberger, Chafee, Grassley, Simpson, and Pressler.

Staff present: Max Richtman, staff director; Jim Michie, chief investigator; Dr. Luis deOrtube, professional staff; Larry Atkins, minority staff director; David Schulke, minority professional staff; and Kelli Pronovost, hearing clerk.

OPENING STATEMENT BY SENATOR JOHN MELCHER

The CHAIRMAN. The committee will come to order.

Today we're going to have the third hearing in less than a year that this committee has held on prescription drugs and what is needed for the elderly in that regard.

There is a particular point we are focusing this hearing on this morning, and that is: adverse drug reaction. We only seem to use the initials around here, and that's what ADR is—adverse drug reaction.

What that means is that a drug that is used causes some type of physiologic reaction in the person taking it that adversely damages the individual.

We take medicine to help, not to have a bad reaction.

The elderly—that is those people in the United States over 65—represent about 12 percent of the population. But of all the prescription drugs that are used in the United States, one-third are purchased by the elderly.

Deaths caused by adverse drug reactions, that were reported to the Food and Drug Administration, amounted to 1,347 in 1987.

The Food and Drug Administration's records showed that slightly over half of those deaths linked to a drug reaction were among the elderly—51 percent. That chart to the right of us there shows that.

And then of those that were hospitalized—4,481 the Food and Drug Administration tells us were hospitalized—over 60 percent were nonelderly, but 39 percent were among the elderly. It is a proportion that is much higher than the elderly population of the country.

So what does that tell us? It tells us the obvious. The elderly, who consume a disproportionate number of prescription drugs and whose physiologic reactions are different from the young, are more vulnerable to adverse drug reactions. It is just that simple. We would expect that. The records show that.

So when we're looking at what we're supposed to be doing here in Congress in Federal programs for the elderly, we have to pay attention to this.

I'm pleased that the Surgeon General, just in the past few days, has completed a workshop on this very subject and has come out with a series of recommendations.

Everyone wants to avoid adverse drug reactions. Doctors prescribing the drugs certainly want to avoid it. Pharmacists that fill the prescriptions certainly want to avoid it. These are their friends, in many instances. And it doesn't make any difference if they're not friends. When the pharmacist fills that prescription for an elderly person it is just human nature to want to be sure that that is a proper drug and a proper drug dosage as prescribed.

Well, we have a little problem here, don't we? That's what the Surgeon General's workshop was about. That's what this hearing is about.

How do we get on top of this problem? Shouldn't we give special attention to prescription drug use by the elderly.

And so we want to start sorting this out, and this is a proper forum to start all of this—before the Special Committee on Aging. It's a special way of doing it and the best way of focusing on this issue is by holding a public hearing.

First of all we want to save lives. That's natural.

Second, we want to save the misery that is caused when there is an adverse reaction. And since the elderly are the group that suffers this the most, it is best to pay special attention to the elderly and the reactions that they are vulnerable to.

And third, we want to save money. And we will save money if we avoid unnecessary hospitalizations and deaths associated with adverse drug reactions.

Now, I think this hearing ought to please the National Taxpayers' Union and all taxpayers across the country to be assured that hearings such as this pinpointing the problems of the elderly are meant for those three purposes I have previously stated: one, to save lives; two, to save misery for the elderly; and, three, to save money. Because there are Federal dollars involved through Medicare and Medicaid, and it is our intention to get a better job done with less money. This is the purpose of this hearing.

[The prepared statement of Senator Melcher follows:]

JOHN MELCHER, MONTANA, CHAIRMAN

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

OPENING STATEMENT

SENATOR JOHN MELCHER
Chairman, Senate Special Committee on Aging

March 25, 1988 hearing

ADVERSE DRUG REACTIONS:

ARE SAFEGUARDS ADEQUATE FOR THE ELDERLY?

Good morning. Today I am calling to order the third hearing conducted by this Committee in less than a year on the elderly and their drug costs. The purpose of this hearing is to highlight the numerous health and cost concerns related to adverse drug reactions within the elderly population, and to explore ways of reducing serious and costly adverse drug reactions and interactions in this particularly vulnerable population.

Adverse drug reactions are costly not only in terms of human suffering, but also in unnecessary and significant expenditures from the Medicare program, the Medicaid program, and from the pockets of older Americans. While the Medicare program currently only covers in-patient prescription drugs, the expected enactment of the new catastrophic health care drug benefit can only increase the amount of unnecessary program expenditures on inappropriate drug therapy and the associated health care required to care for victims of adverse drug reactions.

At the outset of this hearing, it is, of course, important for us to recognize that millions of lives are being saved and prolonged, and many Americans--young and old--spared the ordeal of surgery because of the continuing and increasing revolutionary advances in pharmaceuticals. Since 1976, the FDA has approved more than 1,100 new drugs. Currently, there are more than 10,000 prescription drugs on the market for health care providers to prescribe.

Although older Americans represent only 12 percent of the population, they consume one-third of all prescription drugs. As a result, the elderly obviously stand to benefit most from advances in drug therapy. However, as a disproportionate consumer of these drugs, the elderly also are far more vulnerable to adverse drug reactions and interactions. Beyond the fact that older Americans are more likely to face multiple illnesses requiring multiple drug treatments, the elderly are more vulnerable to adverse drug reactions due to changes in physiological response brought on, at least to some extent, by age.

The elderly suffer adverse reactions at twice the rate of younger adults. The chart to my right, representing reports to FDA on serious drug reactions in 1986, shows that victims 60 years and older -- representing 17 percent of the population -- accounted for more than half of the 1,347 deaths; and 39 percent of the 4,481 hospitalizations. Moreover, these total figures may very well represent the "tip of the iceberg," since most reporting of such reactions to the FDA is voluntary.

Todays witnesses will establish that these reactions often are preventable through appropriate and prudent prescribing by health care professionals in their offices, in hospitals, and in nursing homes. Surveys also show that education of physicians and other health care providers on drug use, especially multiple drug use in the elderly, is not keeping pace with the rapid advances in drug therapies.

Further, as pointed out in recent reports from the Department of Health and Human Services and Institute of Medicine that geriatric training--not to mention geriatric pharmacological training--still is inadequate in our medical schools. Even if the training were adequate, sufficient information about the special needs and problems of the drug-consuming elderly public is not available. Although we are aware of classes of drugs to which the elderly are particularly vulnerable to adverse drug reactions, there are other drugs used predominantly by the elderly that have not been sufficiently studied to determine whether they require special prescribing or monitoring approaches by health care professionals.

To address these shortcomings, I believe the following options should be seriously considered by the Congress:

1. Funding additional studies which focus on methods for providing information to medical personnel who appear to be inappropriately and/or excessively prescribing medications that are known to pose particular dangers to the elderly. Such studies would illustrate how non-intrusive educational outreach programs can reduce the human and financial costs associated with adverse drug reactions and would provide recommendations as to how they could be implemented on a wider scale.

2. Supporting studies on drug categories widely used by the elderly which would provide currently unavailable information on their potential for adverse drug reactions. Such studies could determine whether these drugs should be prescribed or monitored in any special manner.

3. Supporting initiatives which would encourage medical schools to place more emphasis on geriatric training and to provide more information about the special pharmacological needs and vulnerabilities of older Americans.

4. Reviewing FDA policies for approving and updating the drug labels which advise physicians and other health care providers on proper drug prescribing and use. This need

arises because most of these labels contain specific information and warnings for children and pregnancy, but not for the elderly.

5. Strongly encouraging the FDA to publish its long-awaited guidelines for clinical testing of new drugs in the elderly which would require drug manufacturers to determine if a new drug is more likely to elicit an adverse reaction from an elderly person. These guidelines have been in draft form since 1983.

I believe these options have the very real potential to save lives as well as reduce prescription drug costs. According to the American Association of Retired Persons, the elderly population alone spent $9 billion on prescription drugs in 1986, with 81 percent of it coming out of their own pockets. I know that any reduction in this tremendous burden would be heartily welcomed by the elderly. Likewise, I'm sure that the rest of the Congress, the Administration, and the American public would be very interested in something that has the potential to both reduce Federal expenditures and increase the quality of care, as well as the quality of life, for older Americans. This is one of those rare issues where we might very well be able to have our cake and eat it too.

I was particularly pleased to note that the Surgeon General's "Workshop on Health Promotion and Aging," which concluded just two days ago, produced important recommendations on many of the issues that will be raised by our witnesses today. The workshop's "Medication Working Group" came up with 33 recommendations concerning eduction, service, research and policy that, if there is no objection, I will include for the record. Among these 33 "policy recommendations" were:

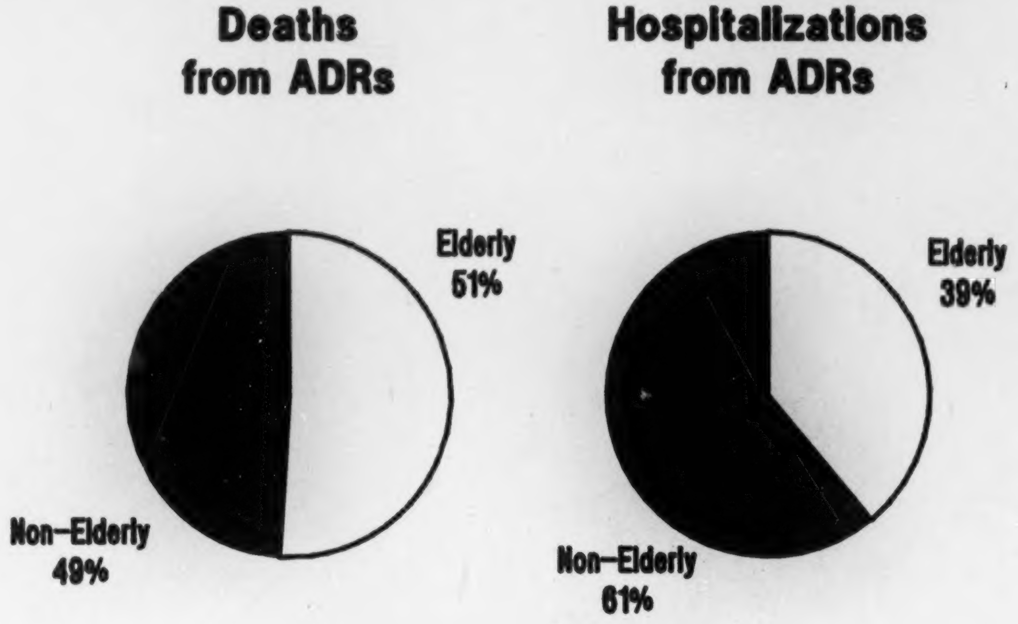
- "New drug labeling should include where appropriate directions for use in the elderly or other subgroups at risk. If no data are available, labeling should state that data are not available."

- "For existing products, label statements regarding use in the elderly should be added incrementally as the label is revised."

- "The use of official drug labeling as a patient teaching tool should be enhanced."

- "The FDA should proceed with final development and implementation of proposed guidelines for development of drugs for use in the elderly, especially elderly subgroups at risk."

I'm looking forward to the testimony of today's witnesses. I know they will give us a clearer picture of the special problems elderly prescription drug consumers face and I look forward to receiving their constructive recommendations on how we should proceed to address this problem.



Deaths from ADRs

Hospitalizations from ADRs

Age 60+ = 17% of Population

Source: Second Annual Adverse Drug/Biologic Reaction Report: 1986
Food and Drug Administration, 1987

The CHAIRMAN. Senator Heinz.

STATEMENT OF SENATOR JOHN HEINZ

Senator HEINZ. Mr. Chairman, every morning some 19 million Americans—older Americans—go to their medicine cabinets, open a few bottles of pills, and innocently swallow medications that are intended to improve their health.

But before this year is out some 300,000 of them will be surprised to find themselves in the hospital simply because they took medicine.

Older Americans have to trust that their doctors and pharmacists know how to make them well. It, frankly, almost never would occur to them—never does occur to them—that the drug regimen that they're on could make them sicker.

Mr. Chairman, I commend you for holding this hearing. It is a hearing, I believe, I suggested to you and the committee staff about 2 months ago. It is a hearing that grows out of work that this committee began in 1983 when I was still privileged to be the chairman of this committee, and it is very timely.

It is time to examine, once again, the life-threatening problem of adverse drug reactions—the ADR's you referred to—in our elderly.

And it is especially timely because Congress is on the verge of enacting a national prescription drug benefit program under Medicare.

As we move for the first time to make it easier for the elderly to purchase drugs, we have to be extremely, acutely aware of the special risks they have of improper medication.

Older Americans, indeed, are the most vulnerable to adverse drug reactions, primarily because they are far more likely to be taking more than one drug at one time.

Millions of aged hospital patients, nursing home, and boarding home residents take an average of six—an incredible number—six medications a day. And even the average older American, the one that isn't necessarily in a hospital or nursing home, the one that is living at home, indeed, consumes an average of four medications a day.

And it is in the light of that risk that it is absolutely astonishing that so many of the very people we rely upon to provide safe and effective medication—namely the prescribers, the physicians, themselves—in fact, lack the knowledge they need to properly prescribe drugs for the elderly.

Why do I say that? Well, in many cases physicians are not adequately trained in medical school, or they simply graduated from medical school at a time before most of these drugs were invented.

In 1983, at the first hearing on this subject that we had under my chairmanship, we found that 70 percent of the physicians graduating from Pennsylvania medical schools and treating Medicare patients flunked a basic test on geriatric pharmacology.

Now, how is it that physicians are getting information? Physicians, it would appear, are relying very heavily upon drug product labeling to tell them about the risks and side effects. This can be dangerous, and even deadly, because, unfortunately, only 3 of the top 24 drugs the elderly use—3 out of 24—are labeled with specific warnings about adverse drug reactions in the elderly.

Worse, still, the FDA—the Food and Drug Administration—appears to be in exactly the same laid-back—I would call it "supine"—posture they were in 5 years ago, when at that time the promised to issue clinical guidelines for testing of new drugs and the elderly.

Here we are 5 years later, and they're no further along. And I'm concerned that the FDA is proving by its absence here today—they were invited, I believe, Mr. Chairman, they did not appear—that they have not appeared because they don't want to explain to us, to this same committee, what they have been doing with this promise—their promise of a policy—for the last 5 years.

Now, in contrast, while the FDA has been dragging its feet, the Surgeon General has commendably shown some leadership on this problem. And on Wednesday, as Chairman Melcher noted, the Surgeon General's workshop on health promotion and aging reported its formal recommendations on medication use by the elderly.

I am particularly interested in hearing comments from our witnesses today on five of the recommendations. The five that I would particularly like to hear about are: First, that new drugs should carry warnings on the labels, including direction for use by the elderly, or indicating if no data on hazards affecting the elderly are available; second, existing drugs should have information regarding use by the elderly added to the label; third, the FDA should implement its guidelines for clinical testing of drugs in the elderly, especially subgroups at risk; fourth, all medical professional schools should include courses on basic concepts of pharmacology— especially risk and efficacy of drugs and the aged; and, fifth, Medicare's drug utilization review program should emphasize education of professionals and should be carried out through professional and collegial contact.

Mr. Chairman, I think we stand poised on the edge of a new era in drug therapy for the elderly. The challenge before us is very clear: we have to ensure not only that the Medicare beneficiaries can afford the medications they need, but that the medications that they take aren't going to make them sick or kill them.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Heinz.

You're absolutely correct. The Food and Drug Administration was asked to testify. They didn't find it convenient.

But I want to say this about the Food and Drug Administration: they are a professional group. They do a lot of good work. But sometimes if you want to get them stirred up, you're going to pass a law. People sometimes wonder why Congress passes so many laws. Maybe this is an example. We're going to have to pass a law outlining for the Food and Drug Administration what they should do in this area.

I also want to point out that what has been reported as deaths from an adverse drug reaction may not be the total; an fact, it probably is not. You know, deaths are reported and causes of death are reported. Sometimes the very specific cause that might have been brought about by first of all an adverse drug reaction may not be identified as truly the cause of death. It may have only been contributory. And that goes the same for that figure there that has to do with hospitalizations involved from somebody taking a prescription drug and having a bad reaction from it.

Senator Shelby is next.

STATEMENT OF SENATOR RICHARD SHELBY

Senator **SHELBY**. Thank you, Mr. Chairman.

I would like to begin this morning by commending you, Mr. Chairman, and the committee staff for holding this hearing today to discuss a problem which affects so many of our elderly citizens. Every year thousands of seniors suffer from adverse drug reactions—reactions which, to a large extent, can be prevented through improved informational programs designed to educate physicians and other health-care providers about the efficacy of the drugs which are prescribed.

Today researchers have made great strides in the development of new drugs which are designed to treat and cure a variety of illnesses.

Members of the health care delivery system must strive to keep pace with the rapid development of these new pharmaceuticals.

It is imperative that a physician understand how the medicine he or she is prescribing will affect his or her patient. This is particularly true when the patient is elderly.

The problem of adverse drug reactions is especially pronounced, as most of us know, among the elderly.

Mr. Chairman, as you well know, the elderly utilize the health care system to a far greater extent than any other group.

Although seniors comprise only 12 percent of our population, they account for approximately 30 percent of all national health expenditures. Due to their greater use of health services, they are most likely to receive prescriptions.

As I understand it, Americans age 60 and older consume 39 percent of the 1.5 billion prescriptions written in 1984. Those seniors over 65 years of age accounted for consumption of 32 percent of these drugs.

These figures do not include the use of over-the-counter drugs, which has been shown to be prevalent among senior citizens.

To compound the problem, elderly individuals are often taking more than one drug. It is estimated that over 6.7 million seniors are taking more than three prescription drugs. One-third of patients in nursing homes receive eight or more drugs daily. Multiple drug use is just one of the factors that predispose the elderly to the risk of an adverse reaction.

Medications are prescribed to benefit the patient, yet elderly patients are more likely to suffer injury resulting from drug therapy than any other persons.

Adverse drug reactions occur at twice the rate in persons age 60 to 70 than those aged 30 to 40, and seven times more often than individuals age 70 to 79 than those aged 29.

An adverse reaction to a drug poses many threats to the elderly patient. The most obvious and important is the danger to their health, already weakened by some ailment the medicine was prescribed to treat.

In addition, the victim of an ADR must bear the financial cost as well. People over 60 are hospitalized more than twice as often for adverse drug reactions as those under 60, and the average hospital stay is almost doubled when a patient suffers from an ADR.

The financial burden is born by the patient, Medicare, and Medicaid, to pay for health services which should not have been needed.

Adverse drug reactions are preventable in most cases.

Physicians, pharmacists, and the patients themselves must understand the proper use of the prescribed medications. Education is the most effective means available to achieve this desired end.

Drugs frequently prescribed for the elderly should contain specific warning labels, as those often prescribed for pregnant women and children.

The Food and Drug Administration should require that FDA-approved drug labels advising physicians and pharmacists on the proper use of a drug contain specific information addressing the special needs of elderly patients.

Physicians, pharmacists, and the patients should work together to avert the injurious effects of an adverse drug reaction.

Education, as I said, is the key. Advances in science and drug therapy will be of no practical use to anyone if we do not possess the knowledge to use them effectively.

As Benjamin Franklin once said, "An investment in knowledge pays the best interest." I can think of no better investment than one which can save elderly patients suffering, financial cost and perhaps their lives.

The elderly segment is the fastest-growing segment of our population. America will continue to age—especially as the baby boom generation matures.

In 40 years it is estimated that one-third of our population will be over age 55. As larger segments of our population age and advancements in pharmaceuticals continue, we will face an even greater challenge to provide safe and effective medications.

Again, Mr. Chairman, I commend you for holding this hearing and for addressing such an important issue.

The CHAIRMAN. Thank you, Senator.

Senator Domenici.

STATEMENT OF SENATOR PETE DOMENICI

Senator DOMENICI. Thank you very much, Mr. Chairman, and thank you for calling this hearing.

I understand, as has already been said here, that the elderly are admitted to hospitals at three times the rate of younger people because of drug toxicity, and hospital stays may even be increased as much as 20 percent due to adverse drug reactions.

Today we are going to hear testimony from senior citizens who have suffered from adverse drug reactions, as well as representatives of the nursing home and medical communities, on efforts to prevent such problems among the elderly.

Among the solutions, obviously, we must consider: increased drug related research, which has been mentioned; greater communication among pharmacists, doctors, and nurses; more comprehensive drug labels and better information on the inserts that are contained in the dispensation of drugs.

And, finally, I'd like to talk about one that I choose to call, outreach education programs to ensure that health care professionals are kept updated on the latest available technology and efforts of prescription drugs.

Research into the effects of drugs on the elderly has only recently been considered essential. For years the effects of tested prescription medication on younger individuals was assumed to be indicative of its effect on the elderly. Precautionary labeling, while already in use, may need to be expanded to include even more age-specific data.

But an avenue of prevention that shows great promise, and about which I'm pleased to talk for just a few minutes, is the area of outreach education.

I'm proud to say that at one of our universities, the University of New Mexico, we are very fortunate to have one of the best elder health education programs in the Nation, the New Mexico Geriatric Education Center at the University of New Mexico.

I know that the committee and the committee staff will find the testimony from that center, which we are going to submit for the record, very helpful and very useful.

With funding that we have been able to obtain from the Public Health Service, the medical and educational communities in my home State joined to establish this center several years ago. It is one of only a few in this Nation, and it helps train geriatric health-care providers, while incorporating their expertise into a formal educational curriculum at the University of New Mexico.

Continuing education for health-care providers is essential, and this New Mexico Geriatric Education Center is a national leader in that area.

The center provides continuing education courses for geriatric health professionals throughout New Mexico, and other professionals who come from 12 other States and Canada. The center provides a valuable working knowledge of the effects of drugs on the elderly.

This New Mexico Center has developed three model long-term care facilities in the immediate area, and in these facilities health care providers have now achieved a 30 percent reduction in medication usage, usually resulting in better health results for the patients.

Multiple drug consumption at these facilities is around three medications per day, comparing very favorably with the national average of over nine per day.

I'm very optimistic, Mr. Chairman, that when we have completed these hearings that this committee will agree that education and drug reduction belong together, and that, indeed, we ought to become advocates of the establishment of this kind of center throughout this Nation. This is a way to bring together the very best, and to reeducate, if you will, those who are already delivering professional health care but are not familiar with the changing times and the changing problems that we are discussing here today.

I am pleased to submit a report from this center to the committee today. No one will be here today to deliver it, because that could not be arranged. But you agreed that it could be made a part of the record. I think this approach is one that we ought to seriously support as a committee.

Thank you, Mr. Chairman.

[The prepared statement of the New Mexico Geriatric Education Center follows:]

New Mexico Geriatric Education Center

University of New Mexico
Albuquerque, New Mexico

New Mexico Highlands University
Las Vegas, New Mexico

New Mexico State University
Las Cruces, New Mexico

NMGEC

Mark A. Stratton, Pharm.D.
Project Director

Paula D. Thomas, M.S.N., R.N.-C.
Project Coordinator

March 23, 1988

Senate Special Committee on Aging
SD-G41U
United States Senate
Washington, D.C. 20510-6400

Dear Senator Melcher:

Enclosed you will find a copy of written testimony for the hearing scheduled for Friday, March 25, 1988. We have attempted to address the issues concerning the topic of the hearing: "Adverse Drug Reactions: Are Safeguards Adequate for the Elderly?"

We would like to thank you and Mr. Chris Jennings for the opportunity to respond to his invitation for written testimony.

Sincerely,

Paula D. Thomas

Mark A. Stratton, Pharm.D.
Assoc. Prof. of Pharmacy
Project Director, NM GEC
Co-chair, Board of Directors, UNM CARES

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cc: Senator Pete Domenici

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PREPARED TESTIMONY FOR THE SENATE SPECIAL COMMITTEE ON AGING

ADVERSE DRUG REACTIONS: ARE SAFEGUARDS ADEQUATE FOR THE ELDERLY?

Mr. Chairman, we appreciate the opportunity to present testimony concerning the issue of adverse drug reactions in the elderly. The elderly are admitted to hospitals at three times the rate of younger people as a result of drug toxicity, and hospital stays may be increased by as much as 20% due to adverse drug reactions. This is due to age-related increased sensitivity to the medications, and to the confounding effects of concurrent diseases and the increased numbers of medications that these patients take. At least 80% of our elders consume one or more medications per day. Studies have revealed that the average older person living at home has four chronic health care problems and takes 3.2 medications per day. Patients in long-term care facilities may take as many as 9.3 medications each day. Clearly, the elderly patient is at increased risk of suffering an adverse drug reaction.

Drug related research is essential in this patient population if we are to decrease the risk of adverse reactions. Other important components of a comprehensive solution to the problem are considerations of precautionary labelling, and improved and expanded education of prescribers (physicians, nurse practitioners, and physician assistants) and for pharmacists who are often called upon by older persons to recommend over-the-counter medications.

From a research perspective we are only beginning to understand the complexities of adverse drug reactions in the elderly. It is clear that we can no longer extrapolate kinetics data from young normal volunteers and apply these data to ill elders. Conducting drug related research in the elderly is currently difficult to accomplish. Abuses which occurred in years past have made elders and their families skeptical of medical research and have sensitized administrators to the ethical issues of drug related research with institutionalized, cognitively impaired elders. However, it is only through research that we will be able to understand the complexity of this issue and begin to design drug regimens that are appropriate for older patients. Only then will we be able to adequately determine the likelihood of an adverse drug reaction and balance this likelihood against possible therapeutic benefit.

The research that has thus far been done in the elderly suffers from a lack of consistency in research protocols. Also, because of physiological and cognitive impairment, it is frequently difficult to consistently assess response to a medication. This is true from an efficacy as well as a toxicity viewpoint. While the Food and Drug Administration has attempted to provide a definitive statement regarding conduct of drug studies in the elderly, this information has not been standardized. Consistent protocols, increased awareness among health care professionals and the public of the importance of such research, and ethical guidelines for researchers and providers would help to overcome the current deficits in drug related research in the elderly. The increasing numbers of older people and the increasing number of available therapeutic agents call for a definitive plan of action that can be set in motion at the earliest possible time.

Another approach identified by your committee, the use of precautionary labelling, could alert prescribers about possible untoward effects in the elderly and could be an effective deterrent to the inappropriate use of medications known to cause problems specifically in elders. It is known from research published in 1987, that elders suffer a greater risk of falls and resultant hip fractures if they are prescribed long acting anti-anxiety agents or long acting anti-psychotics. Alternatives to these long acting agents are currently available and should be the drugs of choice if such medications are necessary for an elderly patient. This is not currently the case for all classes of drugs, but significant headway is being made. Certainly, current restrictions imposed by the FDA regarding the use of many medications in pregnancy or in the pediatric population have been effective deterrents and have prevented many pharmacological catastrophes. Precautionary statements and the resultant increased liability associated with the use of known dangerous medications in the elderly would be a strong deterrent to prescribers.

An equally important avenue to the resolution of this problem is the provision of high quality educational programs and innovative models for teaching health care of the elderly patient. In New Mexico we are fortunate to have one of thirty-one Geriatric Education Centers in the country. The goals of the Geriatric Education Center Program are to improve faculty expertise in geriatric health care and to ultimately incorporate this expertise into existent curricula. The health science schools specifically targeted to benefit from the New Mexico GEC are: The Colleges of Pharmacy and Nursing and the School of Medicine at the University of New Mexico; the Graduate Social Work Department of New Mexico Highlands University; and the Undergraduate Social Work Program at New Mexico State University. The New Mexico Geriatric Center, funded by the Bureau of Health Professions of the Public Health Service is truly a multidisciplinary program designed to optimize the health care of elder New Mexicans. Improved awareness of drug utilization in the elderly is a major part of our program, and is a part of educational preparation of students and of practicing professionals through continuing education.

The parent organization of the New Mexico Geriatric Education Center is the University of New Mexico Center for Aging Research, Education and Service (UNM CARES). This organization represents the entire geriatric/gerontology effort at the University of New Mexico. This organization, through a grant from the Administration on Aging, has already provided continuing education and training for pharmacists, nurses, physicians and others who care for elderly patients. A two-part course entitled "Essentials of Health Care for the Elderly: Clinical Evaluation and Management" was conducted in September 1987, (Session I) and January 1988, (Session II). The first session attracted 339 participants, (76 physicians, 189 nurses and nurse practitioners, 30 pharmacists, and 45 individuals from other health professions including physician assistants). The second session attracted 419 participants and 39 faculty,(93 physicians, 272 nurses and nurse practitioners, 19 pharmacists, 41 medical and nursing students, and 34 participants from other health professions). Participants came from throughout New Mexico, from twelve other states, and from Canada. An important component of these programs was education regarding optimal medication use in the elderly. In the pharmacotherapy sessions monitoring for efficacy and toxicity was stressed, not just for prescribers but for pharmacists and nurses as well. Attendance at this course indicates an awareness on the part of practicing providers of the importance of continuing education in geriatric health care.

At the University of New Mexico we have also developed an interdisciplinary model for providing health care to residents of three long-term care facilities in the Albuquerque area. An important part of our patient care responsibilities is a frequent review of medication regimens and a reappraisal of their appropriateness. As stated earlier, investigators have found that the average number of medications taken by patients in long-term care facilities is 9.3 per day. Our preliminary data suggest that the UNM team prescribes 3.1 regularly scheduled medications per day and 2.9 as needed medications. It is our continuous review of medication regimens that has allowed us to realize a 30% reduction in medication usage. It is important to note that patient function most often improves as a result of careful scrutiny of their medication regimens.

Mr. Chairman, on behalf of elders in the State of New Mexico and the health care practitioners of our State we would like to thank you and the committee for the opportunity to speak to this vitally important issue relating to the health, safety and quality of life of our elders.

Respectfully Submitted by: Mark A. Stratton, Pharm.D.
Project Director NM GEC
Paula D. Thomas, M.S.N., R.N.-C.
Program Coordinator NM GEC
Executive Coordinator UNM CARES

The **Chairman**. Thank you very much, Senator Domenici. We welcome that report. We think it is most constructive and are happy to make it a part of the record of this hearing.

Senator Burdick.

STATEMENT OF SENATOR QUENTIN BURDICK

Senator **Burdick**. Mr. Chairman, I don't have any prepared statement.

I want to thank you for bringing the matter before the Senate. I am particularly interested in how the procedures permit bad drugs to get on the market.

I am assuming that all drugs are tested before they are put on the market. I assume we will go into that area in depth.

The **Chairman**. Senator Durenberger.

STATEMENT OF SENATOR DAVE DURENBERGER

Senator **Durenberger**. Mr. Chairman. Thank you. I have a statement that I would ask be made a part of the record.

The **Chairman**. It will be part of the record.

[The prepared statements of Senator Durenberger and Senator David Pryor follow:]

Adverse Drug Reaction Hearing

Statement by

Senator Dave Durenberger

Mr. Chairman, I want to commend you for bringing our attention to the issue of "Adverse Drug Reactions" for the elderly by holding this hearing and by your leadership in addressing problems of the seniors in this country. It is very important for us to recognize that yearly thousands of elderly experience injurious and costly adverse drug reactions (ADRs) which can be prevented. Unnecessary deaths and costly hospitalizations are also caused by adverse drug reactions. Medicaid, Medicare and the elderly patients themselves pay for these problems, yet the problems can be reduced by improving information and education programs aimed at patients, physicians and other health professionals.

It has been proven that the elderly, representing only 12 percent of the population, consume one-third of all prescription drugs. Older Americans are more likely to face multiple illnesses requiring multiple drug treatments. Due to changes in physiological response brought on by age, these treatments add to the vulnerability of the elderly to adverse drug reactions.

I certainly agree with you, Mr. Chairman, that the FDA should label drugs to advise physicians, pharmacists and other health care providers on appropriate prescriptions and uses (dosage, potential ADRs, adverse drug interactions, etc.). Elderly patients have special needs which require special warnings and precautions on the effects of the drugs prescribed to them as noted by the Committee report. This hearing should help move us toward solving these problems which cause great pain, inconvenience, and waste. Once again, I commend your leadership, Mr. Chairman, and look forward to hearing the testimony of these witnesses.

OPENING STATEMENT

HONORABLE DAVID PRYOR

Special Committee on Aging

March 25, 1988

ADVERSE DRUG REACTIONS: ARE SAFEGUARDS ADEQUATE FOR THE ELDERLY?

Mr. Chairman, I would like to commend you for your work on this committee in the area of drugs and the elderly, and compliment you on the scheduling of our hearing today.

Earlier in this Congress the committee examined issues related to coverage of prescription drugs and the elderly -- a very important topic because our senior citizens are having increasing trouble financing their health care needs. The catastrophic illness package (which is currently in conference committee) will help finance a large portion of the costs for individuals with catastrophic prescription drug bills (above $500 or $600).

However, above and beyond coverage, examination of the area of adverse drug reactions in the elderly is of primary importance in improving the quality of life for many of our senior citizens. Drug reactions can be the result of a number of different problems -- overprescribing, drug substitution, use of expired drugs, combined effects of multiple prescription drugs and/or over-the-counter medications, and misdiagnosis. The problem is exacerbated by the frequent difficulty with which adverse drug reactions are diagnosed. This is a widespread problem, and as the committee data has shown, the results are frequently tragic.

Some adverse drug reactions can't be avoided -- they are a function of individual senior citizens' particular physical makeup. But it is clear that a great proportion of adverse drug reactions in the elderly could be avoided.

Last August I held a hearing of this committee in Little Rock, Arkansas, on prescription drugs and the elderly. Although the main thrust of the subject matter was prescription drug costs, a few of our witnesses chose to focus on drug interactions. One witness in particular, a clinical pharmacist named Cecil Fusilier, spoke quite eloquently of the need for education of our elderly, their relatives, physicians and other health care professionals to the special consideration we must give the elderly where drugs are concerned. He stressed not only problems that arise with prescription drugs, but also with over-the-counter medications, and the need for constant review of drug regimens among the institutionalized as well as "well" elderly. Many local pharmacists are performing these drug regimen reviews as a matter of course for their elderly patients. But I believe much more needs to be done in the area of public educations forums and drug regimen reviews in nursing homes and other institutions, as well as more intensive training for physicians practicing on the elderly.

It's clear that we have a lot of work with respect to public education. But I think we also need to take a closer look at our clinical trials of prescription medications -- it's my understanding that most studies for drug approval by the FDA are performed on young male subjects. I understand that this approach yields the most reliable information on the effects of a particular drug on the population as a whole. However, there are several classes of drugs which are consumed primarily by the elderly -- this must be kept in mind as research protocols on drugs are developed.

Mr. Chairman, once again I thank you for the scheduling of this hearing on this most important subject, and I look forward to the testimony of our witnesses.

Senator DURENBERGER. I regret that I have a resolution on the floor and am going to have to leave in about 10 minutes. But I didn't want to leave without commending you and the ranking member of this committee for your concerns in this area, and also to encourage my colleagues to take a look at the program Pete Domenici has just talked to you about.

A couple of years ago I was lucky enough to see this program in action in New Mexico. I was there for some other reasons, and just happened to come on it because the senior Senator from that State was very proud of the activities engaged in by his people.

I commend to you the lessons that we might all learn from the matter that he has put before us, as well.

Thank you very much, sir.

The CHAIRMAN. Thank you.

Our first witness this morning will be Ms. Ann Little from Gray, TN, who will relate to us her experiences involved with an adverse drug reaction.

Please proceed, Ms. Little.

STATEMENT OF ANN LITTLE, GRAY, TN

Ms. LITTLE. Thank you.

Senator Melcher and members of the committee, I do thank you for allowing me to appear here today to tell my story. It's not a very pretty one, and almost at times becomes one of horror concerning my mother, Donnis Ware. In doing this I sincerely hope to help others in nursing homes—as was mother's case—as well as out of nursing homes.

Donnis lived in Belington, WV, or the surrounding area most of her life. In 1983, on a visit home to help care for my stepfather, I became alarmed, shocked, and deeply concerned when I opened up her kitchen cabinet, which was double-wide, to a mini drug store. Medications were falling out of this cabinet.

Later I emptied out close to 5 gallons of medicines and threw them away.

I couldn't help but think, first of all, this was dangerous to take, as well as to have sitting around. It had been detrimental to her health and to her mind, as you could well see.

Number two, I knew that she was covered under Medicare and a health and welfare benefit plan through a union. She wasn't paying for this, but somebody's money had been wasted.

In this cabinet was an assortment of drugs—across the counter drugs, such as pain buffers, antacids, cough suppressants, laxatives, and such—to numerous—and I do mean numerous—prescription drugs.

Some of these she was taking on a daily basis. They were: Imipramine, 150 milligrams three times a day; Amitriptyline, 50 milligrams; Fldene; Halcion; Besyrel; Xanax; Slow K; Lasix; Lanoxin; Mellaril; Darvocettes; Serox 10 milligrams, 15 milligrams, and 30 milligrams prescribed by the same doctor the same day; Meclizine; Meclomen; Compazine; and Ornade. I hope my pronunciation of these was right.

Early in January 1984, while going through some medical bills of my stepfather versus payments made I discovered something else. I separated these bills and came up with $80,000 in 1983, alone, for my mother. Prescribed drugs accounted for $8,000 of that.

If this was not alarming enough, the same week I took her to Elkins, WV, to a doctor—her physician—for a followup of two hospital confinements. He talked to her for no longer than 4 minutes, and he started writing. When he got to the fifth prescription I was trying to see what was written down, not that I could have understood it, but I wanted to see.

On the seventh one I questioned why so many drugs, and what is the diagnosis, really expecting the worse. His answer was: "Mind your own business. Go back to Tennessee where you belong, and I'll take care of your mother." He was still writing. He never looked up.

Again I tried to question, and was told that the law would be called and I would be bodily removed by the authorities. Needless to say, I left his office with 10 prescriptions, my mother in tow, who was almost to the point of hostility because I had questioned this good doctor's motives that she could go to any time, day or night. She could see him without an appointment. She could call him any time she chose.

On January 17, 1986, I received the dreaded phone call and my fears were confirmed. It was time to face the cold, hard facts. All the paramedic at the station could tell me at this time was that they had found here sprawled across the recliner totally lifeless, incoherent. He couldn't tell me anything else except that they had taken her to the hospital.

Due to severe weather conditions I didn't arrive in Elkins until the next evening. I learned that my mother had overdosed, did not know where she was, why she was there, or even who I was.

My intention was to bring her back to Tennessee and try to get some kind of help. I didn't even know what kind of help, but I knew I had to do something.

I'm not really yet aware of the full circumstances of her admission or how she obtained the new doctor in the area; but apparently it didn't take this doctor but approximately 24 hours to figure out that the illness my mother and he were about to do battle with was drugs in the hospital.

He told me he understood my concern, but if he didn't control the drugs, how did I think I was going to control them. In so many words he told me, "No, you are not taking her back to Tennessee. I am going to admit her to a nursing home here where they can control the administration of her medications."

Now, he didn't say reduce them, he just said control.

On February 28 Mom was still on the same amount of medications that she was given, as prescribed, and on schedule.

At this time, with consulting with the doctor, I was advised to bring her back to Tennessee, start the possible elimination for Alzheimer's disease, which he thought she had.

Also at this time she was taking Sinemet. In August 1985, a doctor told her and told me that it was possible that she had Parkinson's disease. So this was added to the list of medications.

In June 1986, she was diagnosed as early Alzheimer's and a severe behavior problem—not necessarily related to the Alzheimer's.

I realized that I couldn't control the drugs, and I was losing control myself, as well as with her very quickly. So I admitted her—after checking out several nursing homes—to Life Care Center in Erwin, TN. She was placed on the Alzheimer's Disease and Related Disorders Unit, and she remained there for 2 months until they did decrease some of the medications and her behavior became a little bit more controllable.

She was then moved to the ICF Unit.

She is now down—and I think your report says seven medications a day, but as of last day she is down to five medications a day. There are four others that are given P.R.N., but these are monitored very closely.

You know, I can't give her the quality of life that she is getting in this nursing home. I can't do it at home. I couldn't do it at the other nursing home in West Virginia. They were not really interested in getting her off of the medications; only the fact that they be administered the way they were prescribed.

You know, if our Medicare—and in some cases State Medicaid programs and Health and Welfare benefits—can pay $80,000 a year to create this Friday the 13th that they created for me and her as well and her health, why can't we put this money to good use and have some kind of means to control and educate doctors, pharmacies, and nursing homes not to do this.

I thank you.

The **Chairman**. Ms. Little, that is a rather shocking recitation of the number of prescriptions given to your mother. Do you have any particular advice, based on that experience, you'd like to pass on?

STATEMENT OF SENATOR JOHN CHAFEE

Senator **Chafee**. Mr. Chairman. May I briefly interrupt? Unfortunately, I have got another conflict. Might I submit a statement here at the beginning, just for the record?

The **Chairman**. Certainly, Senator Chafee.

Senator **Chafee**. Thank you.

[The prepared statement of Senator Chafee follows:]

STATEMENT BY
SENATOR JOHN H. CHAFEE
AT
THE SPECIAL COMMITTEE ON AGING
ON
ADVERSE DRUG REACTION AMONG THE ELDERLY

MARCH 25, 1988

Mr. Chairman, I commend you for holding this hearing on this very important issue. When we pass the Medicare prescription drug benefit, this issue will become even more important.

The miracles of modern medicine have made life more comfortable and more enjoyable for countless older Americans. Conditions that were once completely debilitating -- like chronic high blood pressure -- can now be controlled with the proper drugs.

But all too often, drugs are unintentionally misused, often with tragic results. For a number of reasons we will be hearing about today, elderly individuals must take particular care when using medications. Physicians and pharmacists sometimes do not communicate effectively with a patient and unfortunately, this can lead to misunderstandings about how a drug should be used.

I hope today's hearing will shed light on this important problem.

The **Chairman**. Senator Grassley, would you have——

Senator **Grassley**. I have a statement that I would submit, yes, Mr. Chairman. And I'm also going to ask questions. But I'll wait until my turn comes.

The **Chairman**. All right. Thank you.

Ms. **Little**. I'm sorry. I lost you there.

The **Chairman**. Ms. Little, you listed 16 different drugs, I believe, at one time. Is how many prescriptions she took?

Ms. **Little**. Sixteen. She ended up with 17.

The **Chairman**. Seventeen?

Ms. **Little**. Yes. She had Sinemet added to this list.

The **Chairman**. Based on that, is your best advice for the elderly just an overall education program? Maybe we have to educate—we can't call upon your mother, who was taking these drugs——

Ms. **Little**. No.

The **Chairman** [continuing]. To discern which ones are not necessary. How do we go about this? You seem to have been thwarted in your efforts to reduce the number until you had your mother placed in Life Care. Is there any better way of avoiding this problem?

Ms. **Little**. There has to be a way with our modern technology. I'm not saying that Mother got all of these prescriptions from one doctor. There were two or three doctors involved.

But the damage was already done, and all this lady could do was look at you and tell you, with this tremor, "I want a pill. Give me a pain pill. Give me an orange pill."

Somewhere this drug store, or some of these doctors, had to know that there was a problem. And what I was mainly interested in, when I administered her in Tennessee and when I did bring her to Tennessee was, "Let's have a little bit of control some way." I finally found this in Life Care.

If it needs to be that she ever can come outside, I do know what to do now. I know that I have a doctor who will watch her medications.

Also, I have a pharmacist—which is the nursing home pharmacist—that plays a key role with the nursing home, as well as the physician, in the administration of the drugs. So we don't have this overlap.

I think that there has to be an educational plan some place, and I think it needs to start with the doctors and the pharmacists.

The **Chairman**. A rather comprehensive educational program among all of the professionals involved.

Ms. **Little**. Right.

The **Chairman**. Senator Burdick.

Senator **Burdick**. Thank you for your testimony this morning.

There are a couple of things I would like to know.

There is no claim here that these drugs are not authorized by the Food and Drug Administration, for example. They were legal drugs at the time?

Ms. **Little**. I'm sorry. I can't hear you.

Senator **Burdick**. Were these drugs approved by the Food and Drug Administration and could legally be used?

Ms. **Little**. Legally I'm assuming they can be used. I don't know. I'm not to this point yet.

Senator BURDICK. I just want to know whether there is some drug in here that has never been approved and involved in the process.

Ms. LITTLE. Not that I'm aware of. Fldene was the only one that I understood at one time that there was controversy about. I did kind of check into that back in 1986.

Senator BURDICK. And they were administered by a physician, a legally authorized physician?

Ms. LITTLE. Yes, sir. They were.

Senator BURDICK. Well, what else could we do. What do you suggest we do about this in the future?

Ms. LITTLE. As I said, any doctor who can prescribe Imipramine and Mellaril together, which I understand is a generic brand of Thorazine—I don't know where this man got his training, but I'm just a common person here with no medical knowledge, but to me that spells trouble.

As I've said, we've got to do something. I'm not really aware of where I need to go for help or how I need to go about it. I feel like I have accomplished something with my mother—believe me—because I have seen a drastic turn around now. You can see more of the Alzheimer's and not this monster.

You can take one and one and get two.

But you take one drug plus another drug and you put them together and you have really created something in some cases.

Senator BURDICK. What I'm interested in is what we can do about it.

Ms. LITTLE. What can you do about it?

Senator BURDICK. What do you suggest we do about it?

Ms. LITTLE. A long range comprehensive study, please. Include your doctors and your pharmacists in it.

Senator BURDICK. I would like to see what the pharmacists and physicians are doing and help prevent this type of problem in the future.

Ms. LITTLE. Yes.

Senator BURDICK. But you just testified that the drug had been approved and administered by a doctor that was licensed.

Ms. LITTLE. Yes, sir.

Senator BURDICK. Well, I don't know where to go from there. That's my problem. I'd like to help. I think the story you have told is shocking. But what do we do?

Ms. LITTLE. I don't really have the answer to that. The only thing I had the answer to—or felt like I had the answer to at the time—was to get her out of the circumstances and get her some place. That's all I could do.

I couldn't bring charges against this doctor, and I can't say that it was one doctor in particular. As I said, she is from a small town. She would go to this doctor at 10 in the morning; at 1 in the afternoon she would go to another doctor. She lived directly across the street from a clinic. She would call over the clinic, the PA, his assistant, is saying, "I can't prescribe a drug for you, but I will call the doctor and tell him the symptoms," and this same doctor is writing the same drug.

I have in Mr. Domenici's office two empty medicine bottles that were written in the same day by the same doctor. One was filled in

Elkins, the other one was filled in Belington. The same drug. The same doctor.

Senator BURDICK. Did your mother see more than one doctor?

Ms. LITTLE. She saw more than one doctor, but they did belong to the same group. It was a group of five doctors.

Senator BURDICK. And they all prescribed the same thing at the time?

Ms. LITTLE. What it was is; she would go in and one doctor would prescribe these drugs. As I said, she would see another one, and he would tell her, "Donnis, throw away the medicine that you got from Dr. So-and-so. I am rewriting this." What he was doing was duping it.

She had another symptom, so he has added another medicine in there. Mama didn't throw it away. It was clutched in a little paper bag or a shoe box with a rubber band around it, and you didn't dare pick it up. You did not pick it up.

Senator BURDICK. I think we're holding these hearings to see how we can prevent this from happening again.

Ms. LITTLE. Yes.

Senator BURDICK. That is why I would like to know what you suggest for the future. What can we do?

Ms. LITTLE. Educate your pharmacists, your physicians, and your nursing homes as well. Educate them to the problem in the elderly. Show them how they can reduce it.

It can be done, as it has been done in the nursing home that Mom is in. Her drugs have been eliminated better than 70 percent. Better than 70 percent.

Senator BURDICK. In other words——

Ms. LITTLE. She is not taking—as I understand now she is taking one psychotropic drug, and the milligrams are very low on that. The other medications are: One is for dizziness; one is for a bladder inconsistency, which is associated with the Alzheimer's.

Senator BURDICK. Then it is your contention that doctors and nurses in this area are not adequately trained?

Ms. LITTLE. They are not. They are not.

The CHAIRMAN. Ms. Little, would part of this be avoided if the labeling on the drugs warned that the overlapping or the counterbalancing of the various drugs involved with the elderly might be harmful?

Ms. LITTLE. It may help in some cases, but I'm sure in my mother's case it wouldn't have.

The CHAIRMAN. It would not have helped?

Ms. LITTLE. It would not have helped her, because this problem apparently started back several years ago. As I said, she didn't read this label on this drug bottle. She didn't even know what she was taking. It was just reach down in here and give me a pill. Get a pill out. She didn't care what she was taking it for. She would take the same pill for a headache as she would for dizziness.

So it may help in some cases, but it's not going to help in hers.

The CHAIRMAN. The education program, though, that you mentioned for pharmacists and physicians in treating a patient such as your mother, also would require that they review very stringently what she is taking, wouldn't it?

Ms. **Little**. Yes. And this is being done now. Her medicines are reviewed.

The **Chairman**. Thank you.

Senator Grassley.

STATEMENT OF SENATOR CHARLES GRASSLEY

Senator **Grassley**. Ms. Little, I don't have any questions of you, but I do appreciate very much your testimony, and am glad I got in on the tail-end of it so that I could hear your real, live experience with problems that this committee is trying to address.

Of course, Mr. Chairman, I compliment you for having these examples. We do need to know how things are really working out there at the grass roots.

Mr. Chairman, even though I don't have questions of this person and I have submitted my testimony, I'm only going to be able to stay here until 11. But just in case I don't get a chance to ask questions of Doctor Colinger, Avorn, and Simonson, I would like permission to submit those for the record and explain to them, if they are here, that I had a conflict. But I do have some questions I would like to have them answer in writing.

[The prepared statement of Senator Grassley follows:]

STATEMENT OF SENATOR CHARLES E. GRASSLEY AT A HEARING OF THE SPECIAL COMMITTEE ON AGING ON 'ADVERSE DRUG REACTIONS IN THE ELDERLY"

MR. CHAIRMAN, I THINK YOU HAVE CHOSEN A VERY GOOD TOPIC TO LOOK INTO TODAY. I ONLY HOPE THAT WE WILL HAVE NOT ONLY A GOOD HEARING, BUT SOME PRODUCTIVE FOLLOW-UP TO IT.

BECAUSE I MUST SAY THAT ALL OF THE CONCERNS THAT I FEEL SURE WILL BE RAISED TODAY ARE NOT NEW CONCERNS.

IN FACT, IT SEEMS TO ME THAT THE CONGRESS, AND OTHER OFFICIAL BODIES, HAVE INQUIRED INTO THESE PROBLEMS BEFORE ON MANY OCCASIONS. THE BRIEFING MATERIALS YOU DISTRIBUTED TO US PRIOR TO THE HEARING NOTED THAT THIS COMMITTEE HAD A HEARING ON DRUG MISUSE IN 1983.

I KNOW THAT THE 1981 WHITE HOUSE CONFERENCE ON AGING LOOKED INTO THE TOPIC OF DRUG MISUSE AMONG THE ELDERLY. I THINK I CAN EVEN REMEMBER HEARINGS ON THIS GENERAL TOPIC WHEN I WAS ON THE HOUSE COMMITTEE ON AGING YEARS AGO.

SO IT'S NOT A NEW TOPIC. IT'S A GOOD TOPIC. BUT NOT A NEW ONE.

NOW, IT CERTAINLY IS THE CASE THAT WE HAVE MADE GREAT PROGRESS IN RECENT YEARS IN THE DEVELOPMENT OF PHARMACEUTICALS THAT HELP THE OLD, AND, INDEED, PEOPLE OF ALL AGES, OVERCOME ILLNESS AND DISABILITY MORE EFFECTIVELY AND MORE CHEAPLY THAT WAS THE CASE IN PAST TIMES.

WE HAVE ALSO MADE SOME PROGRESS THROUGH LEGISLATION IN RELATED AREAS. IN THE 99TH CONGRESS, WE INCLUDED IN WHAT BECAME PUBLIC LAW 99-660, S. 2489, A BILL INTRODUCED BY SENATOR KENNEDY OF WHICH I WAS A PRIME COSPONSOR AND ON WHICH I HELD A HEARING OF THE SUBCOMMITTEE ON AGING WHEN I WAS CHAIRMAN. THE PURPOSE OF THAT LEGISLATION WAS TO IMPROVE THE TRAINING OF PHYSICIANS IN GERIATRICS.

UNFORTUNATELY, DISPITE THE FACT THAT WE HAVE BEEN CONCERNED ABOUT MANY OF THE SAME PROBLEMS WE WILL HEAR ABOUT TODAY, WE DON'T SEEM TO BE ANY CLOSER TO IMPROVEMENT IN ANY OF THESE MATTERS THAN WE WERE WHEN I WAS ON THE HOUSE AGING COMMITTEE YEARS AGO.

WE HEARD THEN:

- OF OVER-MEDICATION, PARTICULARLY OF NURSING HOME RESIDENTS,
- OF MULTIPLE DRUG USE BY THE ELDERLY WITH THE ATTENDANT PROBLEMS OF DRUG INTERACTIONS,
- OF POOR PATIENT COMPLIANCE WITH PRESCRIPTION DRUG THERAPIES,
- OF PHYSICIANS WHO ARE LESS THAN WELL-INFORMED ABOUT HOW DRUGS AFFECT THE OLD,
- OF ADVERSE DRUG REACTIONS OF VARIOUS KINDS

THAT IS WHY I SAY, MR. CHAIRMAN, THAT I HOPE THAT THERE IS SOME FOLLOW-UP TO THIS HEARING, SO THAT THE NEXT TIME WE REVIEW THIS AREA WE CAN POINT TO REAL ACHIEVEMENT.

IN ANY CASE, THIS IS A GOOD SUBJECT FOR THIS COMMITTEE TO TAKE UP, AND I APPRECIATE THE OPPORTUNITY YOU ARE PROVIDING US TO REVIEW WHERE WE ARE ON THESE PROBLEMS NOW.

THAT IS ALL I HAVE FOR THE MOMENT, MR. CHAIRMAN. I LOOK FORWARD TO THE TESTIMONY.

The CHAIRMAN. All right. Thank you. We will submit them in writing for you, Senator Grassley.

[The questions prepared by Senator Grassley are included with other questions that were incorporated into followup hearing letters sent by Chairman Melcher to Dr. Avorn, Dr. Colinger, and Dr. Simonson. These letters and letters of response can be found in appendix, p. 128.]

The CHAIRMAN. Thank you very much, Ann, for your testimony and your willingness to share with us a very bad example of overuse of prescription drugs.

Ms. LITTLE. Thank you. I wish you all the success in the world.

The CHAIRMAN. The next witness is Ms. Wilda Henry from Golden Gate, FL.

STATEMENT OF MS. WILDA HENRY, GOLDEN GATE, FL.

Ms. HENRY. Senator Melcher and committee, I don't take pleasure in having to bring up this situation again, since it has been quite a trauma to me when I have had a very active mother, and in such a short period of time I have a vegetable. But I am doing this for the main reason of helping others that are in a position such as she.

Prior to her illness of organic brain syndrome Mother was 83 years old and was very active for her age. In her earlier years she had owned two restaurants. She lived in Naples at the time she became ill. She was semiretired at that time, did housework in homes, and drove her own car.

Beginning in November 1986—you'll see this is a very short period. It isn't a long time like the last one. This all happened so fast. In November 1986, I noticed that she was doing odd things like calling and asking what day it was. Maybe a half hour later she would call and ask me again what day it was. She would start out in the car and get confused and drive until she could find her position. It has been known of her to call my aunt and give her location and ask her where she is, and they have gone and picked her up.

So in December 1986, she was picked up for speeding—71 miles an hour in a 35-mile zone. Her excuse at that time was, "I'm running out of gas and I was hurrying to the station." So at this time I had her license taken from her to stop the driving.

This upset me. You never know what can happen nowadays.

Finally, in February 1987, I admitted her to Naples Community Hospital. She was cared for by a psychiatrist, neurologist, and internist. They did a full workup and examination on her and the primary diagnosis was organic brain syndrome. The doctor said that she needed constant supervision in a nursing home.

I searched and searched for a nursing home. There's no way we would afford a nursing home at $3,000 a month.

I finally got her into Medicaid then.

When she was discharged from the hospital, the doctors prescribed for her trip to the nursing home 1 milligram of Haldol as needed, and one-fourth milligram of Haldol three times a day as needed after she had been admitted to the nursing home.

It wasn't easy to find a nursing home with a Medicaid bed, but I did find one in Venice, FL, which was about 100 miles from where I live.

I got her into the nursing home in Venice in February—February 27. It seemed like a nice place. It was a beautiful facility. It was clean and neat.

I called her every day from home and talked to her. When I would call I would first ask them her condition before I talked to her, and I was told she was doing just fine.

Four days after she was admitted to the nursing home, on March 2, they had rushed her to the Venice Hospital. They asked me to come right away. I chartered a plane and was there in a half hour.

I found Mother in the emergency room. I asked her what had happened, and she said she didn't know. She said she got sick and vomited. And this was all that I could ever get out of her.

I was there many, many hours. I asked the emergency room doctor what was wrong with her. He said, "Sometimes older peoples' hearts stop beating, and then it just starts beating all by itself and really no reason."

There's nothing else you can say. This is what they say, and that's that.

So Mother was admitted to the Venice Hospital. She was there for 2 days, and did fine. Then she was returned to the nursing home on March 4.

I called every day and visited Mother on the weekends during March. I noticed that she began to have tremors or shakes—whatever they want to call it. I know now what I would call it.

She had always fed herself and she enjoyed going down to the nursing home dining room because she liked to mix with people. The next time I went I noticed that she was—I was shocked to see it—she was tied into a wheelchair and drooling and was wet.

There was one other time I had gone in to see her after she got out of the hospital. I asked if I could take her out to eat, and they said yes. So I took her out to eat, and the first thing she did when they served her food was just start eating with her hands. This is not my mother.

But, anyway, I was shocked to see her in that condition. That was around March 12.

I later went up—and my aunt went with me and a friend of my mother's who Mother used to work for. That was on March 30. I stopped at the administrator's office because the whole time she had been there I had never talked to an administrator or anyone in the offices at all. It always seemed as if they weren't available.

So March 30 we also found her out in the hall strapped in a wheelchair, and she was drooling and wet. My aunt and this friend walked right by her in the hall and they didn't even know her, she looked so bad.

In 5 weeks time I had a mother that went from a very active lady to a vegetable. When I found her this last time like this I went to the phone and I called my doctor in Naples and I started to talk to him. He said, "Wilda, get her out of there as fast as you can." He said, "I know what they're doing to her. I don't even want to hear any more about it. Bring her to me as soon as you can."

So I took her to the hospital in Naples and she was completely out of it. She knew none of us. She didn't even know we put her in the van to bring her home. She didn't know anything. She was completely out.

We got her to the Naples Hospital and the same nurse that was on duty when Mother was being evaluated—it was one of the nurses that came down to help us with her—said, "This is not Cecile, is it?" I said, "That's her." She said, "I cannot believe it."

By the way, I have pictures here that were taken before she went in and when she left the Venice Hospital.

So the doctors then said that—after they saw her, the doctor at the hospital said to me, "The damage is done." I then found out that she had liver damage and had the early stages of Hepatitis. There was a note in Mother's medical records made by her doctor at the hospital on April 5 that reads—it started out that they were giving her B-12, and she was "getting frequent large doses of Haldol, 2.5 to 5 milligrams at one time. She continued to be agitated and combative." That was the report that the hospital gave me when I removed her back to Naples.

So Mother was given no more Haldol then at Naples, and she got somewhat better. While in the hospital she began to eat again, and the shakes never went away. She still has the shakes. Don't get me wrong—they are cut down, because she had been shaking so badly she couldn't eat. She now can feed herself.

The doctor said she definitely is suffering from liver damage caused by the Haldol.

Mother was in the hospital until May 1 when she was transferred to another nursing home in Naples.

Gentlemen, that's it.

The CHAIRMAN. Ms. Henry, the 5 months you described were November, December, January, February, and March. November and December 1986, and January, February, and March 1987; is that correct? Those 5 months?

Ms. HENRY. That's right.

The CHAIRMAN. And your mother went from an active woman——

Ms. HENRY. Very active woman.

The CHAIRMAN. Very capable of taking care of herself.

Ms. HENRY. In fact, when we took her in the hospital for evaluation in the beginning they had to posey her in the bed all of the time because she was either wanting to wash the walls in the bathroom or do some kind of work.

The CHAIRMAN. And then at what point was Haldol first prescribed?

Ms. HENRY. When they put her in for evaluation she would get combative in there because she wanted to get up. If they poseyed her down she got furious.

Then a psychiatrist said that just a little bit of Haldol will calm the mind down so she can think better.

The CHAIRMAN. Well, that was 1 milligram a day.

Ms. HENRY. About one.

The CHAIRMAN. Is that correct?

Ms. HENRY. I'll tell you here in a minute. Yes. That's right. One a day. And then——

The **Chairman**. Routinely? One milligram a day?

Ms. **Henry**. Yes. And then PRN I think was one-quarter.

The **Chairman**. One-quarter?

Ms. **Henry**. Yes.

The **Chairman**. Oh. There is another drug that was prescribed at that time?

Ms. **Henry**. No. Before my mother ever went to the hospital you couldn't even get an aspirin down her, let alone a pill. Of course, that is liquid.

The **Chairman**. Well, as I read your testimony on this particular time it was 1 milligram as Haldol.

Ms. **Henry**. Okay. That was when she was transferred to Venice. He gave her the 1 milligram for the trip.

The **Chairman**. I see. And then every day after that one-fourth milligram of Haldol three times a day?

Ms. **Henry**. If needed.

The **Chairman**. That was in the hospital?

Ms. **Henry**. That was in the hospital. Yes. Then, when she went to Venice, that was February 27.

The **Chairman**. Now, according to the records at the nursing home after the 27th, your mother received a greatly increased dosage of Haldol—sometimes as much as 20 milligrams per day?

Ms. **Henry**. Correct.

The **Chairman**. Now, is it your contention that the increased dosage of Haldol caused extreme damage to your mother's health?

Ms. **Henry**. Oh, yes. She constantly now complains of the pain up in through here, and, of course, that's the liver situation.

The **Chairman**. Liver damage?

Ms. **Henry**. Yes. And the hepatitis was—that was no doubt there. You could tell it. A layman could tell that.

The **Chairman**. After about 31 days of that—or 33 days of that—you brought your mother——

Ms. **Henry**. Back to Naples.

The **Chairman**. Back to Naples? To the hospital?

Ms. **Henry**. Yes. Correct.

The **Chairman**. And no more Haldol from that point on?

Ms. **Henry**. No.

The **Chairman**. And while there has been some improvement since that time, your testimony is to the effect that the heavy dosage of Haldol had caused her liver damage and health deterioration of some——

Ms. **Henry**. Oh, yes.

The **Chairman** [continuing]. Some magnitude. Thank you very much.

Senator Grassley.

Senator **Grassley**. Mr. Chairman, again I appreciate this lady's testimony, particularly because it is an actual one for us. But I do not have any questions for her. I will save my time for the other witnesses.

The **Chairman**. Senator Simpson.

STATEMENT OF SENATOR ALAN SIMPSON

Senator **Simpson**. Mr. Chairman, I thank you.

Mr. Chairman, I want to thank you for the sincere effort you do make to cover the spectrum of these issues of the elderly. It certainly is a great effort on your part and the part of the staff, and I want to be a contributor to the effort and not be obdurate and aggressive. I do intend to participate. I have in the past, and I will do more.

Thank you for this timely hearing on the potential for adverse drug reactions in the elderly. It is something that intrigues me greatly, having practiced law for 18 years and seeing people seriously affected by this.

I have a mother-in-law in a nursing home at the age of 87. My own parents are 90 and 87 and require intensive care. It is a very serious problem.

I see your remarks and have listened to some of them. I thank you for that. These concerns with your mother are very real.

What steps do you think we can do and use to prevent this? We have such a diverse senior population. Some people—you indicated your mother had never even taken an aspirin. That was the way she was and the way she lead her life. Then she suddenly came to this Haldol usage. Some people carefully read the prescription material. Some people even go to the drug store and get the pharmacological report. Others don't do anything—they just take it and say nothing, or take one and go to another doctor and get another thing. I've watched that when I was practicing law.

It was a small town. I'd go and I'd say, "Doctor, do you know that lady brought in a prescription to me the other day? Let me tell you what it was." And he would say, "What. I can't believe it." And then I began to check around and you'd find that true. It's a very real thing, and destructive—terribly destructive.

But I guess, without taking additional time: what do you think, as a concerned, loving daughter, the Federal Government should do here? What should we do?

[The prepared statement of Senator Simpson follows:]

STATEMENT BY SENATOR SIMPSON
ADVERSE DRUG REACTION HEARING
SENATE SPECIAL COMMITTEE ON AGING
MARCH 25, 1988

I THANK THE CHAIRMAN FOR THIS TIMELY HEARING ON THE POTENTIAL FOR ADVERSE DRUG REACTIONS IN THE ELDERLY. THIS IS A REAL CONCERN FOR MANY OF THE ELDERLY WHO NEED TO TAKE PRESCRIPTION MEDICATIONS ON A DAILY BASIS. THIS KIND OF HEARING HAS THE POTENTIAL TO TAKE FULL ADVANTAGE OF THE OVERSIGHT CAPABILITIES OF THIS COMMITTEE. MOREOVER, WITH THE IMMINENT CREATION OF A DRUG BENEFIT UNDER THE MEDICARE PROGRAM, IT IS IMPERATIVE THAT WE REVIEW THE POTENTIAL PROBLEMS THE ELDERLY MAY CONFRONT IN TAKING ANY MEDICATION AND THE MECHANISMS AVAILABLE TO PROTECT THEM FROM INAPPROPRIATE OR EXCESSIVE DRUG USE.

THIS IS NOT TO QUESTION THE NEED FOR PRESCRIPTION DRUGS, THEIR BENEFITS IN SAVING LIVES AND HELPING US TO LIVE LONGER ARE WELL DOCUMENTED. NOR CAN WE BLAME ANY ONE PARTY, SUCH AS THE PHYSICIANS OR DENTISTS, THEIR'S IS A PROFESSIONAL JUDGEMENT THAT COMES WITH EXPERIENCE IN "PRACTICE." RATHER, ANY BALANCED DISCUSSION WOULD HAVE TO REALIZE THE RESPONSIBILITY OF ALL PARTIES INVOLVED: THE PATIENT, THE FAMILY OF THE PATIENT, THE HEALTH CARE PROVIDER, THE PHARMACEUTICAL COMPANIES, AND THE FEDERAL AGENCIES. INDEED, THIS IS A COMPLEX ISSUE THAT REQUIRES CONSIDERATION OF ALL ASPECTS OF THE PROBLEM AND POTENTIAL SOLUTIONS.

WE ARE INDEED IN AN AGE WHERE THE ADVANCES IN HEALTH CARE TECHNOLOGY ALLOWS US TO LIVE LONGER AND ENJOY OUR REMAINING YEARS TO A GREATER DEGREE THAN EVER BEFORE. HOWEVER, THIS MARVELOUS TECHNOLOGY IS A DOUBLE-EDGED SWORD. IT ALLOWS US TO LIVE LONGER BUT IT MAY SURPASS OUR ABILITY TO MONITOR NEW ADVANCES AND THEIR ADVERSE EFFECTS.

IN ADDITION, AMERICANS EXPECT A GREAT DEAL FROM THEIR HEALTH CARE PROFESSIONALS. THEY ARE SEEN AS HEALERS AND PROVIDERS OF MIRACLE DRUGS AND MACHINERY THAT WILL TAKE CARE OF EVERYTHING. THESE EXPECTATIONS MAY LEAD TO A CERTAIN COMPLACENCY. PEOPLE WANT TO BELIEVE THAT THE REVERED "GOOD OLE DOC" WILL TAKE ON THE RESPONSIBILITY FOR FINDING A CURE. UNFORTUNATELY, THIS BELIEF ALSO TAKES THE RESPONSIBILITY FOR HEALTH CARE AWAY FROM THE INDIVIDUAL.

EDUCATION OF THE ELDERLY MAY THEREFORE HELP TO REDUCE THE PROBLEM OF EXCESSIVE PRESCRIBING OR ADVERSE REACTIONS BETWEEN DIFFERENT DRUGS. A NUMBER OF STATES CURRENTLY HAVE PROGRAMS THAT EDUCATE THE ELDERLY ABOUT THE PROBLEMS THEY MAY FACE WHEN THEY GO TO A DOCTOR WHO MAY NOT BE AWARE OF THEIR UNIQUE REQUIREMENTS. THE ELDERLY SHOULD KNOW THE POTENTIAL FOR ADVERSE REACTIONS, ASK QUESTIONS AND TAKE RESPONSIBILITY FOR THEIR OWN HEALTH CARE.

THE ELDERLY ARE ALSO A VERY DIVERSE GROUP OF INDIVIDUALS, WITH VARYING NEEDS. THERE IS NO "TYPICAL" REACTION TO DRUGS FOR ELDERLY PERSONS. I TRUST WE WILL NOT FALL INTO THE HABIT OF THINKING THE ELDERLY CAN ALL BE LUMPED INTO THE SAME GROUP AND WE CAN FIND "A RIGHT WAY" TO MEDICATE ALL OF THEM.

EDUCATION OF HEALTH CARE PROFESSIONALS IS ALSO IMPORTANT. AS PEOPLE LIVE LONGER THEY HAVE MORE MULTIPLE AND CHRONIC DISEASES. IT DOES TAKE AN INCREASED AWARENESS ON THE PART OF THE HEALTH CARE PROFESSIONAL TO KEEP UP WITH THE LATEST DEVELOPMENTS AND KNOW DRUG INTERACTIONS AND THE PROBLEMS POSED BY GERIATRIC MEDICINE. WE WILL HEAR ABOUT SOME OF THE "OUTREACH" PROGRAMS THAT ARE DESIGNED TO EDUCATE OUR HEALTH CARE PROFESSIONALS.

THERE IS ALSO THE FOOD AND DRUG ADMINISTRATION. I AM TOLD THEY WERE NOT EXPECTED TO BE AT THIS HEARING, BUT WE WILL HAVE AN OPPORTUNITY TO HEAR OF THEIR EFFORTS AT FUTURE HEARINGS, WHEN WE WILL HAVE A MORE COMPLETE EXAMINATION OF THE PROBLEM AND POSSIBLE SOLUTIONS. I TRUST THE FDA WILL BE GIVEN ADEQUATE NOTICE SO THEY CAN BE AVAILABLE FOR THOSE HEARINGS.

AGAIN, I COMMEND THE CHAIRMAN FOR CALLING THIS HEARING. THIS IS A COMPLEX AND IMPORTANT ISSUE FOR THE ELDERLY. IT INVOLVES A GREATER AWARENESS OF THE HEALTH CARE PROBLEMS ASSOCIATED WITH GROWING OLD AND THE ABILITY OF OUR MIRACULOUS TECHNOLOGY TO OUTPACE OUR ABILITY TO COPE WITH IT. I LOOK FORWARD TO A MOST PRODUCTIVE HEARING.

Ms. **Henry**. Gentlemen, I'm here to tell you these nursing homes have really got to have some checking done on them. I'm telling you I know other things also.

You can sit back. I spend a lot of time with Mother now. Believe me, there is not a day that goes by that I'm not there. I'm there every day now. But, of course, she's closer, too. It made it very hard when she was 100 miles away.

I do know that there are drugs given in nursing homes without the OK of the doctor. Now, I know that. I have the proof of it.

So Mrs. Jones is over here and she's just throwing a fit. She's combative. We can't get ahold of the doctor, so we go over to Mrs. Brown's medicine and we get a pill there to settle Mrs. Jones down until we can get ahold of the doctor to repay the bill. I've seen it done.

Who knows? Was that pill for that lady? This could cause her more damage than it could good.

I'm not just here telling you this. I have it in black and white.

But, number one, naturally our nursing homes all need better trained people. There is no way that you people can put one nurse in charge of a whole nursing home and everything be run right as far as the medication. They're just spread too thin. That's all.

Senator **Simpson**. Well, I thank you, Mr. Chairman. Our job is oversight. I think that should be one of our greatest tasks, oversight.

At least last year in last year's reconciliation bill, which we supported, we had greater quality controls for federally reimbursed nursing homes. I think we'll be pursuing that with ever greater care.

It is always stunning to me how you can get people to work in there. Once you've spent your days in there like you have and my wife and I have that is—and then they get paid $6, $7, $10. It often is not enough for what——

Ms. **Henry**. You know what I'm saying, then, don't you?

Senator **Simpson**. I sure do. And I believe what you say when you find a person just thrashing around for hours calling one word.

Ms. **Henry**. That's right.

Senator **Simpson**. And then finally the nurses just—you know, they smile a lot, but they want to figure out how to do something about that person.

Ms. **Henry**. You've got it. That's right.

Senator **Simpson**. I thank you very much.

Ms. **Henry**. All right.

Senator **Simpson**. You're a very effective witness, Ms. Henry.

Ms. **Henry**. Thank you.

Senator **Simpson**. Thank you.

The **Chairman**. Thank you very much.

I'm going to call our next witnesses as a panel. Dr. Colinger has a very busy general medical practice in Erwin, TN. He's also the medical director of the Life Care Center Nursing Home in Erwin, TN.

I'd like to have, as a second member of the panel, Dr. Jerry Avorn of Boston, MA. Dr. Avorn is the Director of the Program for Analysis of Clinical Strategies at Harvard University Medical School, and he's also an associate professor in the school's Department of Social Medicine and Health Policy. He is one of the foremost authorities on the elderly and their use of prescription drugs.

The third member of our panel will be Dr. Simonson, who comes all the way from Oregon. He is a respected authority in the field of geriatric pharmacology.

I'd like to have all three of you approach the witness table at one time as a panel.

Perhaps now we will get some solid, professional advice on what the best steps are to alleviate the problems of adverse drug reactions, the problems of the elderly taking too many different types of prescription drugs, and too much, in some instances, which causes damage to their health.

Perhaps you could lead off, Dr. Colinger, with your testimony.

STATEMENT OF J.W. COLINGER, JR., M.D., MEDICAL DIRECTOR, LIFE CARE CENTER NURSING HOME, ERWIN, TN

Dr. **Colinger**. Thank you, Senator Melcher and committee members.

I really don't know why I was chosen to be here. I am a family physician from a rural area in Tennessee. I have no academic qualifications like my colleagues up here, other than——

The **Chairman**. Well, Doctor, you are chosen because you are out there doing a particularly good job in a nursing home. We stumbled on to that fact. Don't be modest about it. We need your input. We need your experience.

Dr. **Colinger**. Thank you, Senator.

Drug utilization in the nursing home that I work at is an ongoing process where we evaluate initially when an individual comes to our facility on a monthly basis.

I have submitted to you a brief detailing the program which we follow at our facility, and rather than bore you through the details, I will give you some of the highlights.

Using a concurrent review of our drug utilization, we have been able to eliminate 86 percent of psychotropic medications—either reduce or eliminate them. We have been able to maintain a facility-wide medication-per-patient average of 3.1 to 3.7, where the national average is approximately 6.1.

Economically, in Tennessee, if we use those figures extrapolated across the 28,000 nursing home beds in Tennessee, an average cost per medication—and my source on this is Ron Graham, the Director of Pharmacy for Tennessee Medicaid—that translates, on a Tennessee level, to a $15,750,000 savings on medications alone.

You have heard some testimony from two individuals involved with their mothers. And, unfortunately, that is not an uncommon horror story in nursing home facilities.

I think there are ways to eliminate that problem. I will address a little bit of that briefly.

At our facility we have a monthly visit, at which time we visit each patient. We also have a monthly staff meeting in which we focus in directly on drug review. Part of the parameters that we focus in on are duplications of medications. If an individual is on more than one drug of a particular type we ask why, and we try to eliminate one. An example would be two antidepressants.

We address PRN abuse. This is medication that has been prescribed by a physician for occasional use at the discretion of the nurses. You've heard where, perhaps in Florida, this was abused. Or another patient's medication was prescribed for an individual.

We limit the number of medications that are available for as-need use by the nursing staff. And we almost never utilize a PRN for a psychotropic medication. We just don't do that.

We compare their medications with their established medical diagnosis. If their medications aren't justified by the diagnosis we eliminate the medication.

We review anyone in the facility that has more than seven medications at any one time. This chart is reviewed by me, personally, as the medical director and, if necessary, the physician attending is consulted.

We review the use of narcotic medications in our facility.

We also get an average report of the number of patient medications per patient—the 3.1 to 3.5 that we average.

We also receive an ongoing report of the number of patients receiving psychotropic medications. In this regard, one of the things that we've done in our facility is institute a drug holiday for psychotropic medications. For a 7-day period each month patients in our facility on this class of medications are totally taken off of this type of drug for a twofold reason. One is to reevaluate its necessity. Another one is to try to prevent some of the ADR's—adverse drug reactions—that are common with this class of drugs.

Utilizing this we have been successful in removing or reducing 86 percent of this class of medications in this facility.

The question has to come up: Why would a rural nursing home in Tennessee attempt to do this? That question has been battered around. The basic answer is: We believe that this improves the quality of life of our residents.

The nursing home has no financial interest in doing this. In fact, it creates problems for both the physicians and the staff. It is a whole lot harder to chase somebody around wandering around that is disoriented than it is to overmedicate them, but that's not our philosophy. We don't chemically or physically restrain folks. We believe this inhibits their quality of life, and also contributes to a number of their ongoing health problems.

You gentlemen have addressed the primary questions of what do we do about the problem. I would suggest that you need to consider at least four areas.

One has been mentioned by Senator Domenici. It involves physician education and outreach and monitoring. An obvious thing that you could do is add a section on geriatrics to the PDR. That doesn't get around the problem with physicians reading the PDR or physician education. I would second and third your idea that the physicians do need educating in regard to geriatric medication.

I think, also, part of the burden lies on the individual patient and the family member responsible for that patient's care. They need to be educated about polypharmacy. Too many of the patients go from physician to physician. I am in private practice, also, and I know it happens, but I don't always know about it. Family members may or may not know about it. So part of the burden lies on the patient and their family members.

Another aspect of solution to the problem involves facility and pharmacy monitoring—facility monitoring, like happens in our nursing home. We do drug utilization review on a monthly basis. I wouldn't mind seeing that at all as a requirement in nursing home facilities.

Pharmacies are in the same situation as physicians. They are not always the sole source of medication for one individual. Most of them are on computers now. They can punch up a profile. But if a patient goes to other pharmacies, they don't know what the other one is doing.

The fourth aspect of it is Medicaid/Medicare monitoring. Somebody has to have the total picture regarding drug utilization on these individuals. I would assume the people who pay the bills do. It wouldn't be unreasonable to me, as a physician, that the Federal Government would develop a program whereby certain number of medications are approved, certain number of medications are not approved, and a limit placed on total numbers.

If these four areas are not all addressed, something is going to fall through the safety net. You can't just concentrate on physician education. You can't just concentrate on PDR changing their literature. You're going to have to do all these parameters, or else people are going to fall through the safety net and they are going to end up with polypharmacy, as we've heard.

Thank you.

[The prepared statement of Dr. Colinger follows:]

"ADVERSE DRUG REACTIONS:
ARE SAFEGUARDS ADEQUATE FOR THE ELDERLY?"

TESTIMONY

of

J.W. Colinger, Jr. M.D., Medical Director

and

Susie Hutchings, R.N., BSN, Director of Nursing

of the

Life Care Center of Erwin, Tennessee

before the

United States Senate Special Committee on Aging

Senator John Melcher, Chairman

DRUG UTILIZATION REVIEW

The Experience of Life Care Center, Erwin, Tennessee
J.W. Colinger, Jr. M.D., Medical Director
Susie Hutchings, R.N., BSN, Director of Nursing

OUTLINE

I. Introduction
II. Drug Utilization Review
  A. Development of the Problem List
  B. Evaluation of Drug Utilization in Relation to the Problem List
  C. Concurrent Review
    1. Physician - Patient visit
    2. Facility Drug Review
      a. Duplication of medications
      b. PRN abuse
      c. Medication vs diagnosis
      d. Excessive medications
      e. Narcotic medications
      f. Average number of medications per patient
      g. Number of patients receiving psychotrophic drugs
  D. Drug Holiday

1.

Drug utilization review should be an integral aspect of quality assurance in all nursing home facilities. This review process should utilize a multidisciplinary approach which involves the medical director, director of nursing, administrator, and other allied personnel. We at Life Care Center accomplish this review by using a four step process which starts upon the arrival of the patient at our facility and continues concurrently through their discharge. These steps are as follows:

I. Development of the patient's problem list.
II. Initial evaluation of drug utilization in relationship to the problem list.
III. Concurrent drug utilization review.
IV. Initiation of a drug holiday for psychotrophic medications.

I. Development of the Problem List

An accurate determination of each patient's diagnoses and problems upon admission is a critical starting point in the overall management of the nursing home patient. This is accomplished through a careful review of the patient's medical records, by a complete history and physical examination, and by obtaining appropriate laboratory tests.

II. Evaluation of Drug Utilization in Relation to the Problem List

Nursing home patients in particular and the elderly in general are clinically challenging to any physician. As people age most disease processes are increasingly prevalent and the potential array of available medications is complex. Patients suffering from drug side effects and polypharmacy are all too common upon admission to our facility. After a problem list has been developed for the patient, a review of their present medications is performed. If the patient is on unnecessary medications, these are stopped.

III. Concurrent Drug Utilization Review

Drug utilization at our facility is monitored using a two-step approach. Monthly, at the time of the physician-patient visit, medications are reviewed with the director of nursing and any deletions or additions are made. Additionally at our monthly staff meeting, a facility-wide report is given which reviews the following:

1. Duplication of medications - multiple medications being given for the same problem. Example - a patient receiving two antidepressant medications.

2. PRN abuse - medications which are ordered on an as needed basis and are given routinely.

3. Medications vs Diagnosis - the diagnosis does not justify a particular medication.

4. More than seven medications - any patient who is receiving more than seven regular medications has their chart reviewed by the medical director and if necessary is discussed with the attending physician.

5. Narcotic medications - the charts of patients receiving this class of medication are reviewed for appropriateness.

6. A facility-wide report is given for the average number of medications per patient and the previous month's comparison is noted.

7. A facility-wide report is given for the percentage of patients receiving psychotrophic medications and the previous month's comparison noted.

IV. Drug Holiday for Psychotrophic Medications

A drug holiday is a period of time in which a medication is discontinued for the purpose of evaluating continued need and/or to prevent or delay possible adverse drug reactions. In May of 1986 we instituted a drug holiday program for major and minor tranquilizers. A total of 32.6% of our patients were on this category of medication at the onset. At the end of a one week period free of these drugs only 14, or 13.8%, of our patient population were placed back on this class of medication.

DRUG HOLIDAY

May 17, 1986

Life Care Center of Erwin

Larry Hodge, Administrator
J. W. Colinger, M.D., Medical Director
Susie Hutchings, R.N., Director of Nursing

DRUG HOLIDAY

Drug Holiday: A drug holiday is a period of time in which a certain medication is to be discontinued as designated by the physician for the purpose of preventing or delaying adverse reactions of the medication and evaluation of the continuing need for the medication.

Comments by Medical Director: In May of 1986, we at Life Care Center of Erwin have instituted a drug holiday program for major and minor tranquilizers. The rationale behind this is twofold:

1. We wanted to see what impact the elimination of these mind-altering drugs would have on the patient, thereby determining the need for continuation;
2. To eliminate, if at all possible the potential side effect of tardive dyskinesia.

To date, our experience with this program has been very positive. We have found that 57% of our patients taking these types of drugs can be successfully taken off and maintained off these medications.

Rationale: Patients placed on certain types of medications are at a higher risk for developing possible side effects and adverse reactions. The adverse reactions and side effects of antipsychotic agents need to be reduced as much as possible in the nursing home environment. Adverse reactions such as extrapyramidal reactions - neuromuscular reactions have been reported frequently. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness), dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crisis (see attached list of definitions) have been reported far less frequently, but were often more severe.

All antipsychotic agents have been associated with persistent dyskinesias. Tardive dyskinesia may appear in some patients on long term therapy. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. There is no known effective treatment for tardive dyskinesia.

Other CNS effects may include insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, exacerbation of psychotic symptoms including hallucinations and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholenergic drugs.

Catastrophic reactions and temporary agitation do not necessarily indicate long-term maintenance on psychotropic medications. We feel that it is important to evaluate these patients on a monthly basis to determine:

1. Is the medication necessary?
2. Can adverse reactions be avoided or delayed by withholding the medication for a period of time?

It is very important for the well being of the patient to repeat this evaluation monthly and also from a legal standpoint for the physician to determine the necessity for the medication.

If the patient becomes agitated or exhibits symptoms which require the medication, it may be resumed. If the patient does not exhibit symptoms which require the medication the physician is to be notified to determine if the medication should be discontinued.

The length of time that the medication will be held will be specified by the physician.

The order for holding the medication must be given by the physician and he/she must be involved in the continuing or discontinuing of the medication. The Director of Nursing and/or Medical Director is responsible for the explanation of the program to the A.P. (attending physician).

It is very important that all nursing personnel understand the necessity of this evaluation in improving patient care and quality of life. We do not want the patient receiving any more medications than is absolutely necessary. It is also important that the family members understand the necessity of this evaluation.

Plan: The following medications will be discontinued for a specified period of time during each month:

Haldol
Thorazine
Mellaril
Valium

Xanax
Ativan
Amitriptylene
Any other tranquilizers

Procedure:

1. Review each MAR to determine which patients are presently on the above medications.
2. Notify the patient's physician to receive the appropriate order (The total program has previously been discussed with the physicians).
3. The original order is to be written on the chart by the Charge Nurses (see attached copy of order).
4. The order will be printed on the MAR by the pharmacist at the beginning of each month.
5. The medication will be blocked off for the specified period of time by the 11-7 Charge Nurse at the beginning of each month.
6. At the end of the specified period of time the Charge Nurse will notify the physician of the patient's condition will either continue or discontinue the medication and document why in the Nurses Notes.

On May 18, 1986, there were 33 patients placed on a drug holiday. The patients were on the following medications:

Haldol	13 patients
Ativan	2 patients
Thorazine	3 patients
Mellaril	2 patients
Xanax	2 patients
Amitriptyline	6 patients
Surmontil	2 patients
Benadryl	1 patient
Hydroxyzine HCL	2 patients

The Medical Director specified that the patient was to be placed on the drug holiday for 7 days and the attending physician requested 3 days.

A total of 32.6% of our patients were on this type of medication at the beginning of the drug holiday. At the end of one week only 14 or 13.8% remain on those medications. Nineteen medications were discontinued.

General Comments:

In general the response was good. The nursing staff understood the importance of the drug holiday and the purpose and therefore had a very positive attitude. Many of the patients had no change in their behavior. A certain percentage of the patients did exhibit symptoms of agitation and were started back on the medication. In one month's period of time we will once again evaluate those patients. The initial evaluation will give us a baseline to evaluate the patient on this month. We have also discussed tapering the medication off on some of the patients to attempt to at least decrease the dosage if we cannot discontinue the medication entirely. We have also looked at the possibility of placing the patient on a prn medication rather than starting them back on a medication which may cause such adverse reactions.

One case history to note was an elderly female patient who was placed on the medication after several days of being agitated and several nights of insomnia. The patient was resting at night, but was continuing to be loud and agitated during the day on Haldol 0.5 mg bid. It would have appeared that increasing the dosage might have been helpful, but rather when the Haldol was discontinued she became much quieter and much more alert.

Cost Analysis:

Over a one month period of time, this would be a cost savings of $274.27.

Definition of Terms

1. **Antipsychotic Agents:** Any of a group of compounds that calm or quiet an anxious patient.

2. **Extrapyramidal reactions:** Parkinson-like symptoms, motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crisis.

3. **Dystonia:** Impairment of muscle tone

4. **Kathisia:** Fear of sitting down

5. **Hyperflexia:** Overextension of a limb or part.

6. **Opisthotonos:** An arched position of the body with the feet and head on the floor caused by a tetanic spasm.

7. **Oculogyric crisis:** Producing or concerning movements of the eye.

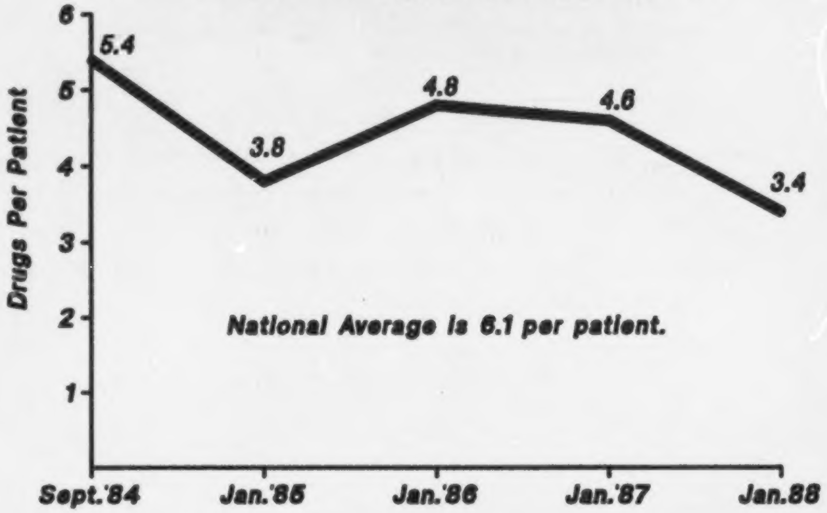
8. Dyskinesias: Defect in voluntary movement.
9. Tardive Dyskinesia: Latent reaction, difficulty of movement.
10. Drug Holiday: A period of time that a specified medication is to be discontinued for the purpose of preventing or delaying any adverse reaction and for the evaluation of the need for that medication.
11. Catastrophic Reaction: Over-reacting to a situation, not understanding what is happening.

The third week of each month discontinue ______________ for 3 days. If the patient becomes agitated or exhibits symptoms which require the medication it may be resumed. If the patient does not exhibit symptoms which require the medication contact the physician to determine if the medication should be discontinued.

V.O. Dr. Bieberly / Carolyn Schu

7 days - Dr. Colinger

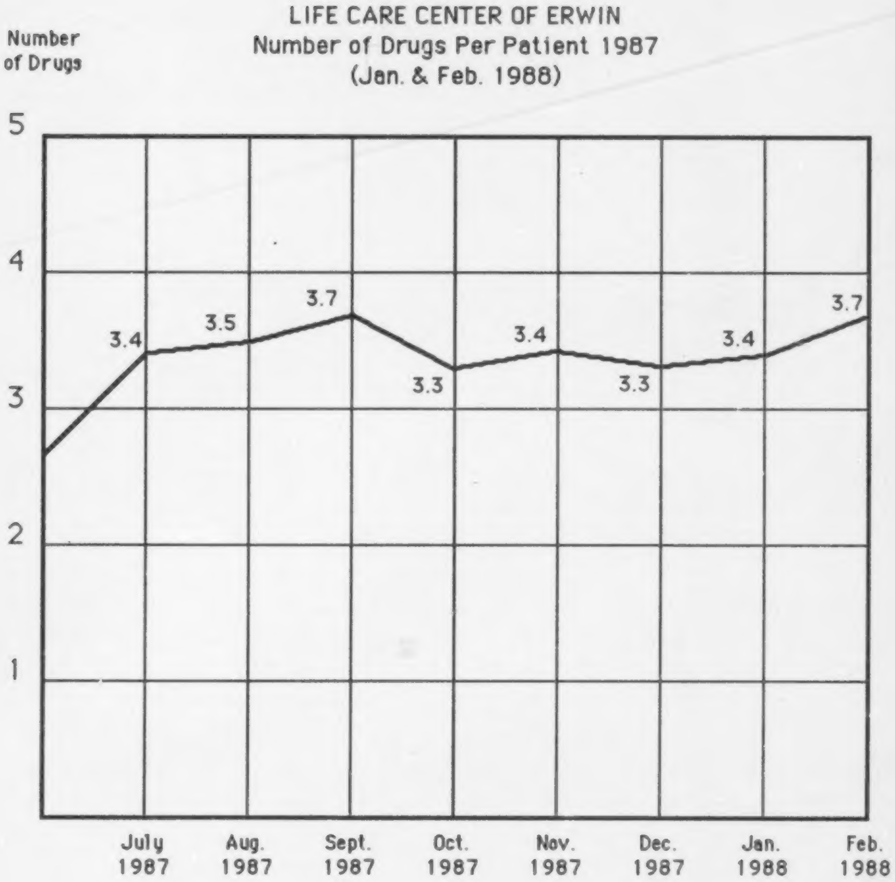
3 days - Dr. Slonaker



Results of "Drug Holiday"
Number of Drugs per Patient
Life Care Center Nursing Home, Erwin, Tennessee

Drug Category	*National Percentage In Nursing Homes*	*Drug Utilization Life Care Center; Erwin, Tennessee March, 1988*
1) Cardiovascular	*21.2 %*	*20.4 %*
2) Psychotherapeutics	*11.7 %*	*6.1 %*
3) Diuretics	*10.0 %*	*3.2 %*
4) Antibiotics	*6.0 %*	*0.9 %*
5) Nutritional Supplements	*4.4 %*	*2.2 %*
6) Hormones	*4.2 %*	*2.2 %*
7) Antiarthritics	*3.4 %*	*0.6 %*
8) Analgesics	*3.3 %*	*1.2 %*
9) Dermatologicals	*2.9 %*	*1.0 %*
10) Bronchial Therapy	*2.8 %*	*1.6 %*

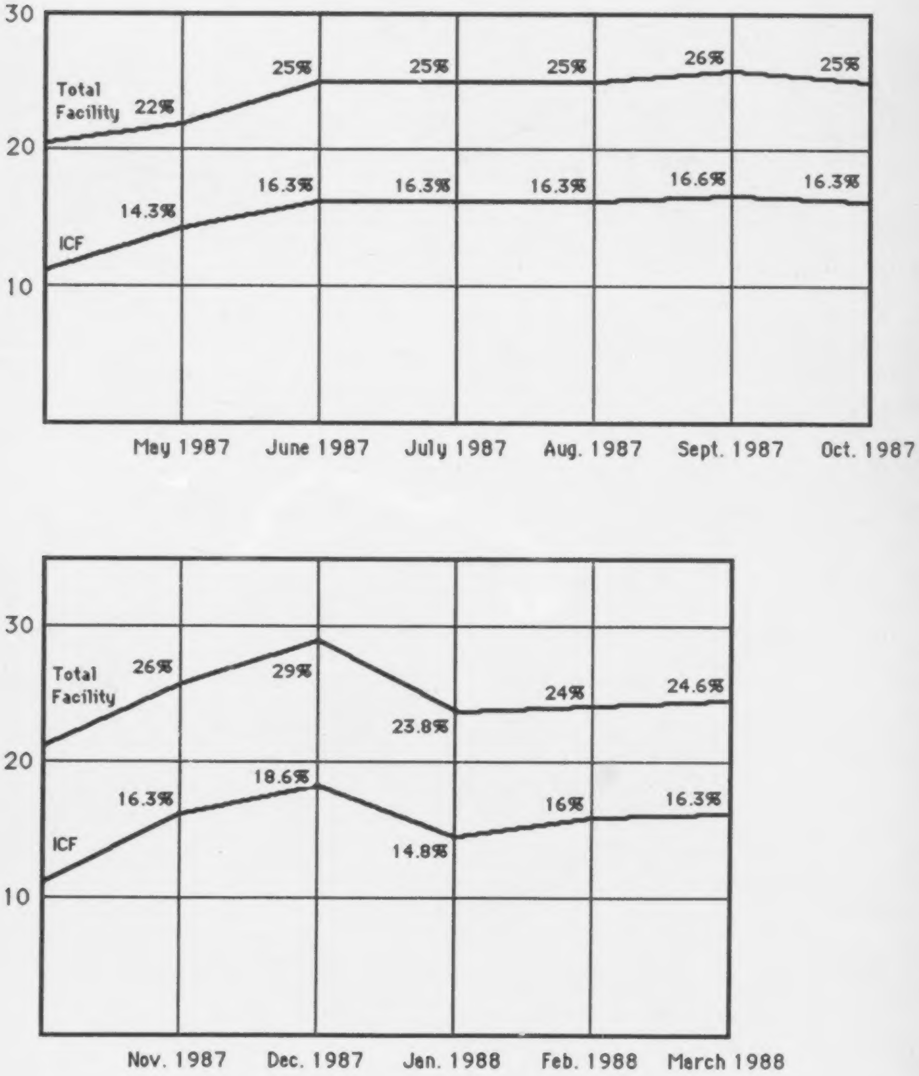
SENATE SPECIAL COMMITTEE ON AGING
"ADVERSE DRUG REACTIONS: ARE SAFEGUARDS ADEQUATE FOR THE ELDERLY?"
MARCH 25, 1988



LIFE CARE CENTER OF ERWIN
Number of Drugs Per Patient 1987
(Jan. & Feb. 1988)

NATIONAL AVERAGE IS 6.1 PER PATIENT

LIFE CARE CENTER OF ERWIN
Psychotropic Medications 1987



LIFE CARE CENTER OF ERWIN

	ICF	AD	Total Facility
(1) Cardiovascular	63	24	87
%	20.4%	15.4%	18.6%
(2) Psychotherapeutics	19	20	39
%	6.1%	12.8%	8.3%
(3) Diuretics	10	4	14
%	3.2%	2.5%	3.0%
(4) Anti-Infections	3	1	4
%	0.9%	0.6%	0.8%
(5) Nutritional Supplements	7	3	10
%	2.2%	1.9%	2.1%
(6) Hormones	7	8	15
%	2.2%	5.1%	3.2%
(7) Antiarthritics	2	3	5
%	0.6%	1.9%	1.0%
(8) Analgesics	2	4	6
%	0.6%	2.5%	1.2%
(9) Dermatologicals	0	4	4
%	0%	2.5%	1.0%
(10) Bronchial Therapy	5	1	6
%	1.6%	0.6%	1.2%

		Life Care Center of Erwin	
Category	National Percentage	June 1987	March 1988
(1) Cardiovascular	21.2%	27.1%	20.4%
(2) Psychotherapeutics	11.7%	4.4%	6.1%
(3) Diuretics	10.0%	7.3%	3.2%
(4) Antibiotics	6.0%	1.2%	0.9%
(5) Nutritional Supplements	4.4%	2.8%	2.2%
(6) Hormones	4.2%	2.8%	2.2%
(7) Antiarthritics	3.4%	3.5%	0.6%
(8) Analgesics	3.3%	1.2%	1.2%
(9) Dermatologicals	2.9%	0.6%	1.0%
(10) Bronchial Therapy	2.8%	1.6%	1.6%

Life Care Center of Erwin

National average drug utilization in Nursing Homes 6.1
Average monthly drug utilization at Life Care Center 3.5
Average cost per drug per patient per month in Tennessee $18.00

6.1
-3.5
2.6

$13.00 cost per drug per patient per month
x2.6 (variance)
$46.80 savings per patient per month
x 28000 patients in Tennessee
$1,310,400 savings in Tennessee per month
x12 months per year
$15,724,800.00 - Estimated cost savings in Tennessee for one year.

Source: Dr Ron Grahm
Director of Pharmacy
Tennessee Medicaid

The Chairman. Thank you very much, Dr. Colinger.

We'll hear next from Dr. Avorn.

STATEMENT OF JERRY AVORN, M.D., DIRECTOR, PROGRAM FOR THE ANALYSIS OF CLINICAL STRATEGIES, DEPARTMENT OF SOCIAL MEDICINE AND HEALTH POLICY, HARVARD MEDICAL SCHOOL

Dr. Avorn. Thank you, Senator.

A point that hasn't yet come up in some of the very cogent testimony we've heard today is why the elderly are at such a great risk of adverse drug reactions.

One very simple reason is that they need a lot of medications very often. We are often dealing with people who are complicated, who have many concurrent illnesses, and who, perhaps, would be dead or severely disabled even further were they not on these medications.

So I would like to put into perspective the fact that many elderly people are living better, much longer lives because of their medications.

But at the same time, they are at much higher risk for developing problems because of some normal changes that we know occur with the aging process, itself.

The elderly body has much more difficulty clearing itself of medications. The liver or the kidney are much less able to get rid of drugs, so that whatever you take, if you are 80, is going to have a much larger effect than if you are 40 or 50 years old.

There are some very, very good drugs out there. The problem is not that we have let drugs onto the market that are bad, as much as the fact that it is very tricky to use them correctly.

As has been pointed out earlier today, many of the physicians who are now in practice have never been systematically instructed in anything about geriatrics, or in anything about the proper use of medications in recent years. They may have learned it in medical school, or they may not have. In the case of geriatrics, they probably didn't. We are still turning out generations of medical students this very day who don't know much geriatrics.

For doctors who finished their training 10 or 15 years ago, many of these drugs were not even on the market then. Thus, there is a tremendous informational deficit that hits hardest at the group of patients who need these drugs the most and who are most vulnerable to their side effects, as well as most able to benefit from them if they are used correctly.

That is the problem, and you've heard it expressed, perhaps better than I can, by some of the earlier witnesses.

Nonetheless, there are solutions that are very do-able; they are not just theories, but programs which have been put into place on a demonstration basis and have been verified as being effective. Some of them represent work that we've done. Other work has been done by groups around the country.

One approach is not just conceptualizing education as something that there should be more of, but actually going out and seeing whether education can change prescribing.

In some work that our group at Harvard did a while back we were able to take advantage of the fact that many pharmacists have great expertise in drug use and can be used to educate physicians as outreach educators, much as Senator Domenici described as being done in his State.

We prepared materials in which we sent out pharmacists from Harvard Medical School to educate physicians about how best to use drugs, and were able to show, in a study that spans four states and many, many months of data, that you can, in fact, reduce inappropriate prescribing.

We are, at present, in the midst of a study which is almost complete that is funded by the John Hartford Foundation, in which we've tried to learn from the drug industry—which is very good at getting physicians to prescribe things differently—how we could perhaps use the same approach to reduce inappropriate prescribing for the elderly.

I have provided the committee with some examples of what have been called unadvertisements that we have prepared in Harvard in order to show a way to get out to the community and reduce excessive drug use.[1]

You have these in the originals. I would like to show you here some which you have in your packet.

This is an unadvertisement that is designed to point out that sedatives can be very bad for the elderly. This one says in the headline, "In the elderly, the side effects of sedatives are all over the map," and we point out that lethargy, falls, confusion, memory loss, and disorientation, are all things which can result from the excessive use of sedatives.

On the back there is some pharmacology instruction that physicians may never have heard before about when not to use these drugs in the elderly. It explains what dose and what appropriate choices should be made if you have to use a drug.

Similarly, this is another unadvertisement that we have prepared at Harvard and are using in our study to reduce drug use in nursing homes. This one says, "Your gentle touch may be all she needs at bedtime," and it is designed to demarket excessive use of sleeping pills in nursing homes.

With the help of our research group we have gone out to 12 nursing homes in Massachusetts to present these ideas—not just to doctors, but also to nurses and the aides, because, as was mentioned, they play a very important role in these drug decisions.

Others of the materials which you have in front of you describe problems related to excessive drug use in nursing homes, relating to confusion, Parkinson's Disease symptoms, and other sorts of adverse effects. Tragically enough, these are often not even known to be adverse effects, but the attribution is, "Well, Mrs. Smith is 88 years old; of course she is incontinent and confused. What do you expect?" when, in fact, it is something that we physicians might be doing to her to make her like that.

The headline on this unadvertisement that we've prepared says, "The sparkle is gone," and the idea here is not so much that somebody may suffer permanent disabling side-effects that result in hospitalization, but rather, they're just not quite the same people. The edge is taken off them. That's a very common adverse effect that I see clinically as a geriatrician all of the time. Mom or Dad just aren't themselves.

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[1] See p. 65.

It turns out, when you look carefully at the medications, Mom or Dad is on a sleeping pill or tranquilizer and antidepressant, and any number of other medications. Many of these are not psychoactive by design, but blood pressure pills, heart pills can also cause very important mental impairments, as well as physical impairments, if they are not used intelligently. If they are used intelligently, they can save somebody's life.

Incontinence is another problem that is often attributed to old age itself, but can be a medication-induced disorder which, if there is enough intelligence on the part of the physician and others caring for the patient, can be cured just by changing the patient's medications.

In summary, there is now evidence hard data that shows that if you do outreach education from a medical center to practicing physicians and pharmacists and nurses and aides about drugs and the elderly, then you can show—and we have shown—that you can reduce excessive use of these medications.

The followup part of the research that we are currently completing is attempting to learn whether the clinical status of patients can be improved, as well. You don't have to prevent too many fractured hips because somebody fell down from too much medication before you can begin to show that this has enormous clinical implications, as well as cost implications.

One can't talk about anything in health care these days without talking about cost. There is, fortunately, some good news on that front as well, and that is that Steve Soumerai—a colleague of mine at Harvard Medical School—and I have looked very carefully at the cost of this program that we mounted to reduce excessive prescribing. The concern was: How can society bear the burden of yet another expense in health care? We have too much expense already.

The good news is that you actually do save more dollars than you spend when you do this. And, again, that's not theory; that's data that we've published in the medical literature.

If you look only at the reduced expenditures that, in this case, Medicaid was spending on drugs that people didn't need and they were getting no benefit from, the amount of money saved by the various Medicaid programs that we worked with in our research was greater than the dollars that it cost to do the program. And that is not factoring in all of the hospitalizations, all the nursing home stays, and all the other clinical events that can be prevented if we are educating people to do better jobs in prescribing.

Not only can this approach reduce a great deal of illness and suffering, it also can pay for itself and save the health care system money by virtue of getting people to simply think more carefully about medications. And the benefit-cost analysis is there.

We have talked with the National Institute on Aging, which has expressed a great deal of enthusiasm about some sort of a national program now that Medicare is going to be supporting drugs for the elderly. At the same time we're putting dollars into the system to pay for drugs, wouldn't it be good if we were also putting dollars into the system to encourage people to use these drugs more intelligently?

Probably that will reduce the use of excessive drugs, and probably it will also reduce some of the adverse drug effects that we've heard about this morning.

Finally, Ms. Little said, when asked if there was something else we can be doing, "There must be something that technology can do to make this better."

On this rein, there is one additional point I would like to raise. The computer has presented us with some very exciting ways of trying to control this problem of misuse of medications in the elderly by us physicians. Specifically, there are two exciting possibilities for combining computers, medications, and the elderly.

One is better surveillance of drugs that are currently on the market. As has been mentioned, we really are not yet testing drugs in any significant numbers in the elderly, although those very drugs are used mostly by the elderly.

That is a problem that does need to be addressed. But while we are addressing it—or until we address it—there is now the capacity to look at large populations of people and all the medications that they are taking. The Food and Drug Administration has moved forward effectively in that regard by supporting a number of groups—including our own—to look at these computer-based systems, many of which are derived from the Medicaid program, and see what relationship there is between drug use and subsequent hospitalizations or other adverse effects.

Finally, there are many programs in the country—and Medicare may become one of them in the next few years—in which it becomes possible to profile all the medications that a given individual is taking and create some flagging system such that if somebody, such as Ms. Little's mother, or some of the other people that we heard about today, were taking many, many drugs from many, many physicians—perhaps through many different pharmacies—it is now technologically possible to flag those people and to go out and say, "Here is a physician that needs some educating, here is a pharmacist that needs to be talked to," and perhaps even, "here is a patient that we might address."

That technological option opens a great window to addressing this in a proactive manner.

Thank you.

[The prepared statement of Dr. Avorn follows:]

HARVARD MEDICAL SCHOOL
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ADVERSE DRUG REACTIONS IN THE ELDERLY:

Causes, Consequences, and Prevention

Jerry Avorn, M.D.
Director, Program for the Analysisis
of Clinical Strategies
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A number of factors have converged in recent years to elevate the use of medications to a position of enormous importance in the care of the nation's elderly. The dramatically increasing numbers of elderly have made them the most prominent consumer of prescription medications; although only 12% of the population, those over 65 consume about 30% of all prescription drugs. As the proportion of elderly in society increases in the next century, and the fraction of the elderly who are in the group known as the "old-old" (85 and up) rises, this trend will continue even more strongly.

Basic science and clinical research have now produced a vast number of powerful and effective new therapies undreamed of in previous generations. Because of our ever-increasing capacity to understand the workings of cells and organs, we have been able to create drugs that can affect the most basic aspects of biological functioning. Because of this, these products can achieve therapeutic benefits which are unprecedented. However, this same power makes them capable of producing a wide variety of adverse drug effects. The elderly are particularly vulnerable to these effects because their livers and kidneys are often less able to metabolize and excrete drugs, their bodies are more sensitive to drug effects, and they are far more likely to be taking a combination of medications and have a variety of potentially complicating diseases as well.

Unfortunately, medical education in the United States has only recently discovered the presence of geriatrics as a subject fit for consideration in medical school curricula. Although beginnings have been made in many parts of the country, it is nonetheless still true that most students graduating from U.S. medical schools today do not receive a systematic or in-depth exposure to the specific problems of diagnosis and treatment in the aged. This is particularly unfortunate since those over 65 account for the largest share of medical problems which physicians are called upon to treat. At the same time, many observers have commented that our preparation of medical students in the use of medications for all age groups falls short of what it should be; this inadequacy persists through post-graduate medical training as well. Thus, physicians in training today are poorly prepared to address the issue of proper drug use in the elderly. Physicians who trained 10 or more years ago received even less instruction in this critical area.

Thus, we see the confluence of several trends: greater and greater numbers of elderly people taking medications which are ever-more powerful, under the care of physicians who have probably not received very much training in the proper use of drugs in the elderly. To some extent, this educational void is filled by the promotional and educational activities of drug companies, but since the ultimate purpose of such communication is to persuade physicians to prescribe a particular product, these activities can not make up for the absence of broad-based, non-commercial education of physicians in this area.

These trends create two clear outcomes. Many more elderly patients are alive and functional today because of the benefits they receive from their medications, and this is an enormous boon to the elderly in particular, and to society in general. However, at the same time we are seeing a disturbing frequency of adverse drug reactions in the elderly that are caused by the improper use of these very medications. Adverse drug effects in the elderly are often not identified as such, since the symptoms they cause are often attributed (incorrectly) to old age itself: forgetfulness, depression, fatigue, and a wide variety of bodily complaints. Indeed, none of these are the result of normal aging, but patients, family members, and even physicians may mis-attribute these symptoms to the onset of aging rather than to a specific medication. Or, even worse, the drug side effect may be mis-interpreted as a new disease (such as Alzheimer's disease, Parkinson's disease, or depression), and an additional drug may be added to the patient's list of therapies to "treat" this new complaint.

There is another important reason for the frequency of adverse drug effects in the elderly, beyond a deficit in physician knowledge. That is the fact that there is no requirement for medications to be tested in the elderly prior to widespread marketing, even though the aged may be the most frequent users of the drug once it is released to the public. Although the Food and Drug Administration has been discussing the possibility of guidelines for including the elderly in pre-marketing tests of drugs for years, no requirement has yet been promulgated, and there has been great variability in the eagerness with which drug companies have sought out the elderly in the investigational stages of a new drug. Indeed, there is an understandable tendency for them to avoid including such patients, since they may be more complex, more difficult to study, and may pose unwanted difficulties in the speedy passage of a drug through its required clinical studies. Nonetheless, the risk that we run by under-representing or ignoring the elderly in this important process is that we might repeat disasters such as that of Oraflex (benoxaprofen), in which widespread use of this drug by elderly patients once it was marketed resulted in unacceptably high rate of side effects and even mortality before the manufacturer voluntarily withdrew it from the market.

The problem is not simply that of under-representation of the elderly in the drug approval process. Because these clinical studies necessarily involve only a limited number of people, a side effect which may occur once in every ten thousand patients may be completely missed, although this would represent a very large frequency if a drug is used on a widespread scale nationally once it is approved. This problem is only compounded by excluding patients who are "complicated" by advanced age or co-existing illnesses, since it is they who are likeliest to experience these side effects once a drug is released in the marketplace.

Despite these problems of inadequate physician information and unanticipated adverse effects, there are some positive steps that can be taken immediately to address both of these issues. First, on the issue of physician education, my colleague Stephen Soumerai and I, together with our associates at Harvard Medical School, have been working for several years on developing methods to educate physicians about the proper use of medications. In brief, we have attempted to learn how it is that the drug industry has been so successful in changing physician prescribing practices, and have attempted to emulate some of the more effective means of communication which they have developed. With support from the National Center for Health Services Research, in 1979 we launched a study designed to take the expertise of medical centers such as Harvard and disseminate it to physicians in their offices through educational-outreach pharmacists (sometimes called "academic detailers").

In a randomized controlled study of 435 physicians that was published in the New England Journal of Medicine in 1983, we were able to show that through the presentation of concise, scientifically valid information to physicians in their offices during short "tutorial" sessions, we were able to reduce inappropriate prescribing by 14%, compared to physicians randomized into the "control" group. In subsequent analyses, Dr. Soumerai and I demonstrated that although such an approach may seem cumbersome and costly, we actually were able to save the state Medicaid programs in the four study states twice as much as it cost to mount the program. This approach has been adopted in several other settings concerned with improving the quality and cost-effectiveness of drug therapy, and we are now expanding this technique to other kinds of clinical decisionmaking as well.

More recently, with support from the John A. Hartford Foundation of New York, our group at Harvard has been funded to look at the problem of medication mis-use in nursing homes, a site of particularly worrisome prescribing for our nation's elderly. Using the educational materials attached below, we have devised a similar program of medical school outreach to physicians as well as nurses and aides who care for patients in the nursing homes. In addition to measuring prescribing change in the homes offered the educational program, we are also measuring whether improvements in prescribing are associated with improvements in the mental capacity of previously over-medicated patients.

Our initial glimpses of the data are very encouraging, but complete analysis of our findings will not be available until the late spring. However, this experience has confirmed our other work in demonstrating that it is both feasible and cost-effective to perform "educational outreach" for physicians and other health care workers in order to improve the precision with which they write prescriptions. As more and more providers of care become interested in the issue of prescription drug use, from Medicaid to the Veterans Administration to HMOs and other insurors, this approach will no doubt gain even more widespread use.

In view of the widely recognized information deficit of many physicians in the area of geriatric pharmacology, it would seem most appropriate for the Department of Health and Human Services to launch such an educational outreach program to physicians at the same time as it begins to underwrite the cost of prescriptions for the elderly. As our research and that of other groups has clearly shown, such a program would save more dollars than it would cost, even if only medication costs are considered. If one looks also at quality-of-care issues and the prevention of adverse effects, the benefits of such a program outweigh its modest costs even further. This approach is also appealing because as an educational activity, it does not resort to coercion, regulation, or the use of financial incentives, which recent experience has shown all too well may appear to be "quick fix" solutions in medical care, but which often produce as many problems as they solve.

On the area of the detection of adverse drug effects in large populations, there is also reason for optimism. The rapidly expanding sophistication and dropping cost of computer technology have made it possible to monitor the medication utilization patterns and clinical experiences of enormous numbers of patients with relative ease and efficiency. Often, an enormously rich body of raw data exists in the paid claims files of programs such as Medicaid, Medicare, the various state-run drug benefit plans for the elderly, and health maintenance organization records. This makes it possible to trace the experiences of tens or even hundreds of thousands of patients exposed to a particular medication and determine whether there is an unexpectedly high rate of a particular adverse effect in such people compared with comparable patients who are not taking this drug. This expanding field of pharmaco-epidemiology is yielding important new insights into the risks and benefits of various forms of drug therapy. This, too, is an area to which our research group at Harvard Medical School has made a strong commitment. With funding from the National Institute on Aging and the Food and Drug Administration, we are developing a database of all medication use and clinical encounters of patients in the Medicaid, Medicare, and Pharmacy Assistance for the Aged and Disabled programs of the state of New Jersey. This makes it possible to follow in great detail the rates of adverse effects associated with the use of various medications in a population which now exceeds a million patients. Drawing together the insights of geriatric medicine, epidemiology, computer science, and health services research, we are attempting to learn how such powerful databases can be used to inform the practice of medicine, particularly in relation to the study of drug effects in the elderly.

Thus, the explosions in both medical knowledge and in the aging of the population provide us with both a challenge and an opportunity to do remarkable things. The inclusion of medication benefits under Medicare offers a window of opportunity to simultaneously introduce an educational program for physicians concerning how best to use medications in this vulnerable age group. Rather than be an add-on expense, there is ample evidence that such pro-active teaching would have net positive economic as well as clinical benefits. Simultaneously, the Department of Health and Human Services through its various branches should intensify efforts to understand the effects of widespread use of powerful new medications in an aging population before we are obliged to learn about them the hard way. The two efforts are complementary, in that greater understanding of the insights gained from drug epidemiology (post-marketing surveillance) could inform the educational efforts, as well as the product information for medications which is approved by the FDA, at present frequently deficient with respect to the elderly. It is not often that we have the opportunity to contain costs and improve the quality of care at the same time: such creative approaches to thinking about the best use of medications in the elderly offers such an opportunity. We should not let it slip by; the elderly of the country deserve far more than that of us.

Senator **Simpson**. Doctor, thank you very much.

Our chairman is voting. We have a rollcall vote now, and Senator Melcher will return in a few moments and I will leave. That is the necessity for his absence.

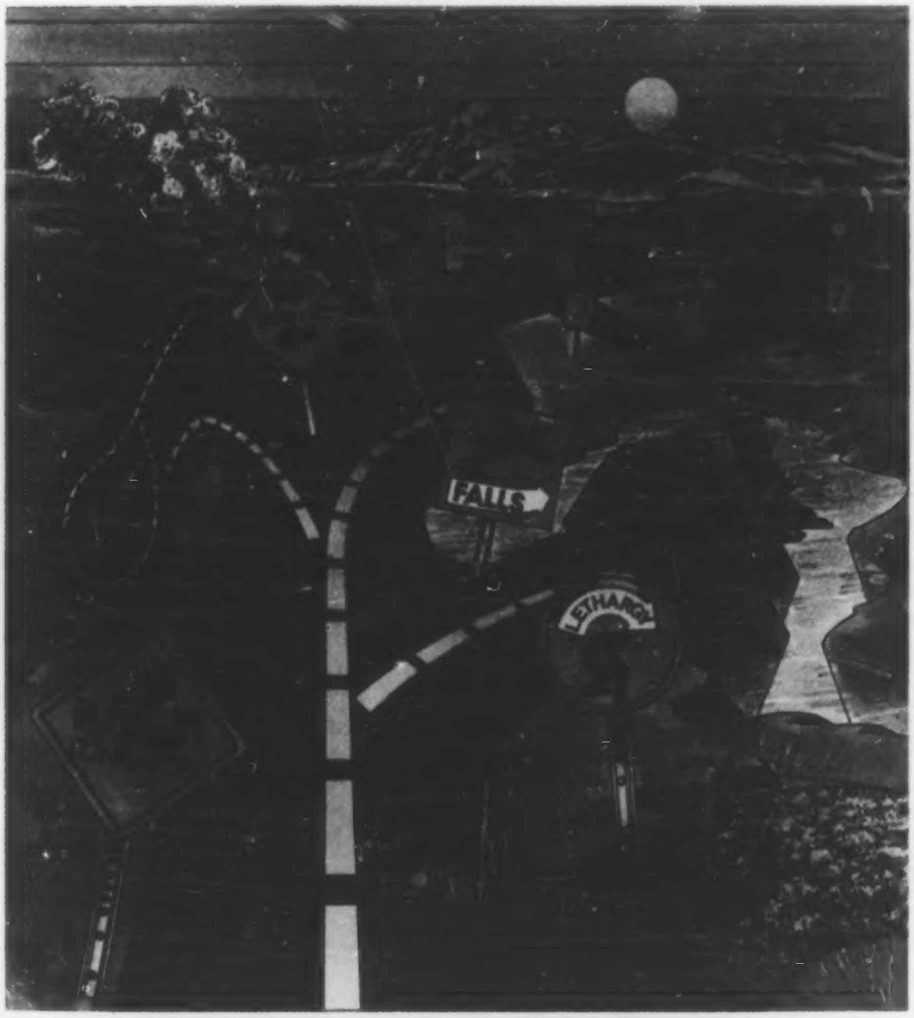
I thank you for your testimony.

I would very much like to have copies of those documents.

Dr. **Avorn**. I would be happy to provide them.

[The information to be supplied follows:]

In the elderly, the side-effects of sedatives are all over the map.

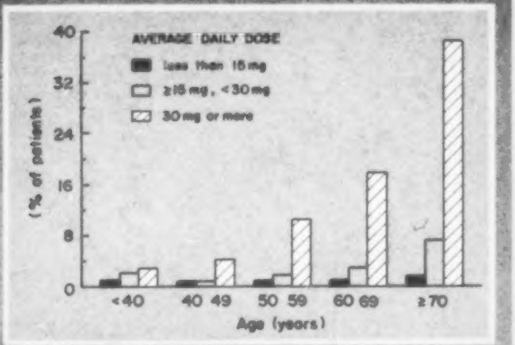


THE SIDE-EFFECTS of tranquilizers can be much more frequent and severe in the elderly. Consider non-drug alternatives first. If drugs must be used, the shortest course is usually the safest course. Choose a medication with a brief half-life, and give it for only a few days or weeks to minimize adverse effects.

[illegible]

[illegible]

[illegible] renal function, the elderly are more likely than younger patients [illegible] sedative drugs.[2] In addition, the aged brain is more sensi- [illegible] psychoactive drugs – another cause of more frequent side- [illegible] tranquilizers and sedatives can cause impaired coordination, [illegible] and confusion as well as a withdrawal syndrome.[3,4]



[illegible] INCREASES [illegible] WITH DOSE AND AGE

The graph reflects the higher frequency of [illegible] a benzodiazepine, flurazepam [illegible], that occurs when it is used in older patients. It also illustrates the reduction in [illegible] reactions seen with use of lower doses.

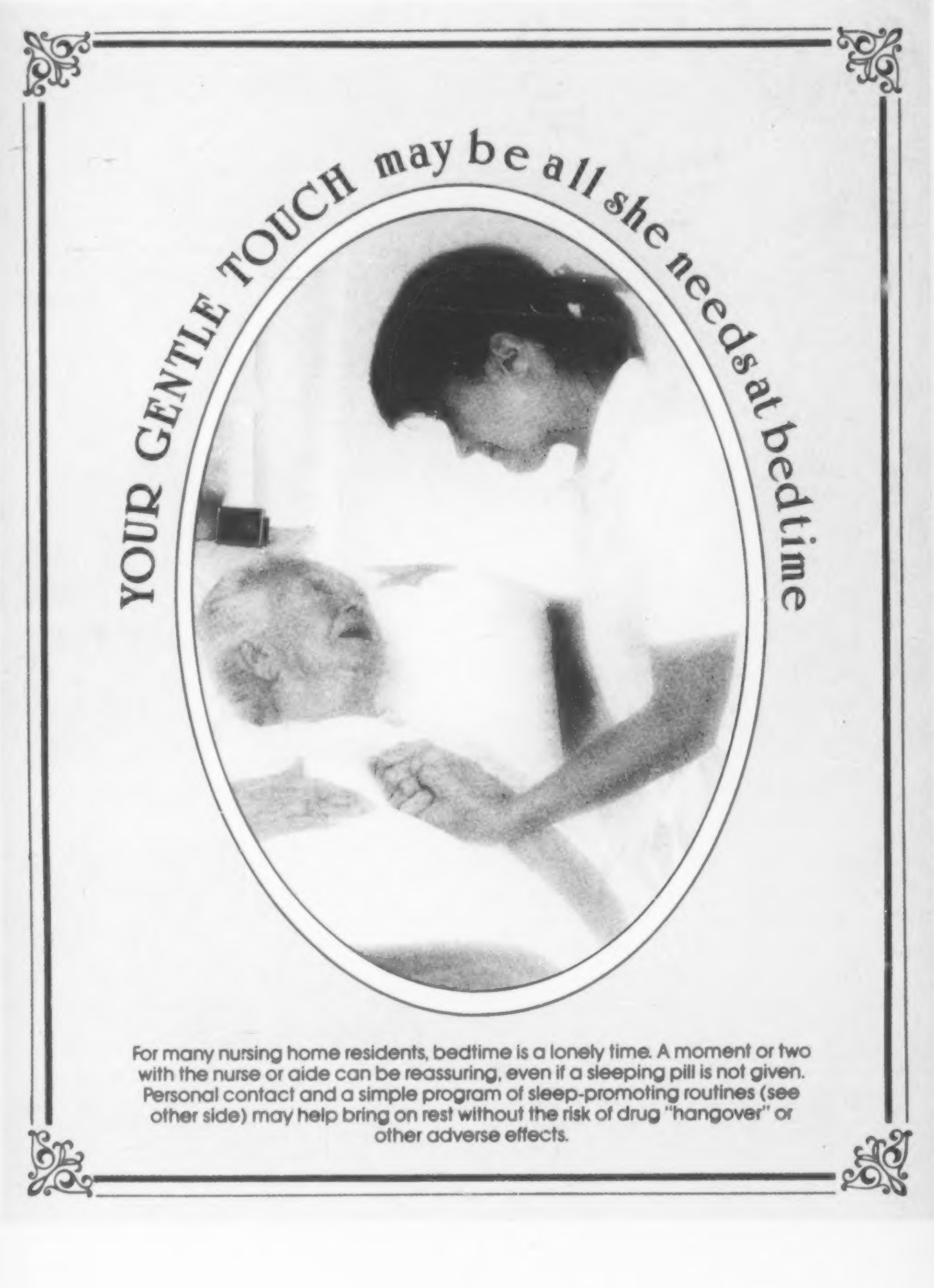
Source: Greenblatt DJ, Allen MD, Shader RI. Toxicity of high-dose flurazepam in the elderly. Clinical Pharmacology and Therapeutics 1977; 21:355-61.

THE GIFT THAT KEEPS ON GIVING
Some sedative drugs such as diazepam (Valium) and chlordiazepoxide (Librium) have very long half-lives in the elderly, and can continue to accumulate and sedate in such patients.[3,5,6] For acute or severe episodes of anxiety, support and reassurance may suffice. But if a drug is needed, one of the newer, shorter-acting sedatives such as oxazepam (Serax) or lorazepam (Ativan) are preferable.[7] **Intermittent and p.r.n. use also help avoid dose-related side-effects.**[5] The dose should be 25-50% of that usually given to younger patients.[7]

LONG-TERM USE OFTEN UNFOUNDED
Many patients on long-term tranquilizer therapy don't continue to benefit from it, but they do continue to be at risk for adverse effects. One prospective study found that fully 50% of patients treated with Valium (diazepam) for chronic anxiety could be switched to placebo with no return of their symptoms.[9] Ideally, the dose should be tapered to zero over a few weeks.

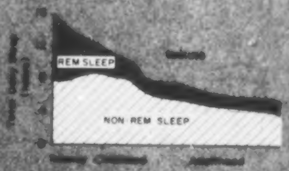
Periods of anxiety do not always require treatment with a tranquilizer; consider interpersonal interaction first. If and when medication is necessary, use
- **a short-acting drug • in the smallest effective dose**
- **on a P.R.N. or intermittent schedule**

[illegible]



YOUR GENTLE TOUCH may be all she needs at bedtime

For many nursing home residents, bedtime is a lonely time. A moment or two with the nurse or aide can be reassuring, even if a sleeping pill is not given. Personal contact and a simple program of sleep-promoting routines (see other side) may help bring on rest without the risk of drug "hangover" or other adverse effects.



As the human being moves from infancy to old age, the total amount of time spent in sleep drops from 16 hours to less than six.[1]

LONGER LIFE, LESS SLEEP . . .

As people age, their bodies seem to require fewer hours of sleep. Studies indicate that although young adults sleep an average of about eight hours a night, the average for the very old is less than six hours per night.[1] Brief awakenings during the night are common and normal for many elderly people.[2,3]

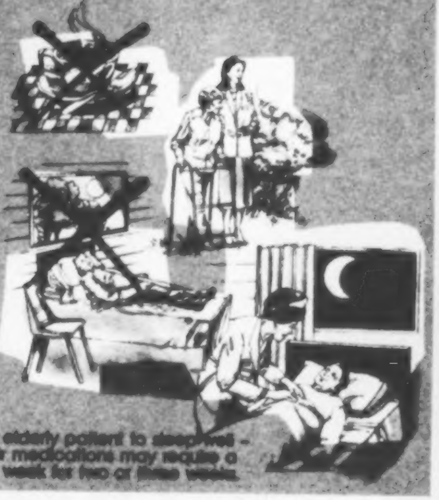
Elderly patients are more likely than younger patients to experience complications from sleeping medications.[4] Some commonly used sleep medications can cause memory loss, confusion, falls, daytime drowsiness, incontinence, and unsteadiness.[5] Patients with any of these side-effects are less safe, require more supervision, and are less able to care for themselves.

Surprisingly, there is very little good evidence that the commonly used benzodiazepine sleep medications continue to work in many patients beyond several weeks of use.[6]

ARE THERE ANY ALTERNATIVES?

A simple program of sleep-promoting routines can help:

- **Avoid caffeine after 2 pm** (coffee, tea, colas – except decaffeinated).
- **Increase exercise and mobility as much as possible.**
- **Discourage daytime napping.** It may be a side-effect of the sleep medication, and only makes matters worse.[7]
- **Keep bedtimes regular and sensible.** An 85-year-old who needs only 6 hours of sleep and is put to bed at 9 pm will be up by 3 am!
- **Help elderly residents to have realistic expectations of sleep.**
- An analgesic at bedtime, such as an aspirin product or acetaminophen (Tylenol) will help patients with chronic pain to fall asleep. It will also comfort those who feel dependent on the idea of a pill at bedtime.
- Take the time for a brief "tucking in" even if no medication is dispensed. **It's a major active ingredient of any sleep program.**



In many cases, a careful program of this sort will enable the elderly patient to sleep well – and safely. Those who have developed a habituation to their medications may require a gradual taper of their drug, reducing the dose by half each week for two or three weeks.

IF A DRUG MUST BE USED OCCASIONALLY: PRESCRIBE IT ONLY WHEN NEEDED . . . NOT EVERY NIGHT.[3]

DRUG	HALF-LIFE (hours)	ANTI-CHOLINERGIC PROBLEMS	GERIATRIC DOSE	COMMENT
oxazepam (Serax)	SHORT 4-8	NONE	10 mg	ok for occasional use
lorazepam (Ativan)	MODERATE 10-20	NONE	0.5-2 mg	ok for occasional use
chloral hydrate	SHORT 4-6	NONE	250-500 mg	ok, but g.i. irritation can occur
temazepam (Restoril)	MODERATE 8-20	NONE	15 mg	ok for occasional use
triazolam (Halcion)	SHORT 2-4	NONE	0.125 mg	elderly may experience hallucinations, amnesia
diphenhydramine (Benadryl)	MODERATE 4-8	**SEVERE**	not recommended	can cause frequent anti-cholinergic Sx
flurazepam (Dalmane)	**VERY LONG** 50-100	NONE	not recommended	duration of effect too long

REFERENCES: 1. Regestein QR. Insomnia and sleep disturbances in the aged. Journal of Geriatric Psychiatry 1980; 13:153-171. 2. Guilleminault C, Silvestri R. Aging, drugs and sleep. Neurobiology of Aging 1982; 3:379-386. 3. Quan S, Bamford C. Sleep disturbances in the elderly. Geriatrics 1984; 39:42-47. 4. Salzman C. Key concepts in geriatric psychopharmacology. Psychiatric Clinics of North America 1982; 5(1):181-191. 5. Meyer BR. Benzodiazepines in the elderly. Medical Clinics of North America 1982; 66(5):1017-1035. 6. Solomon F, White C. Sleeping pills, insomnia and medical practice. New England Journal of Medicine 1979; 300:803-808. 7. Ebersole P, Hess P. Towards Healthy Aging. St. Louis, MO: C.V. Mosby, 1985; pp. 227-228.

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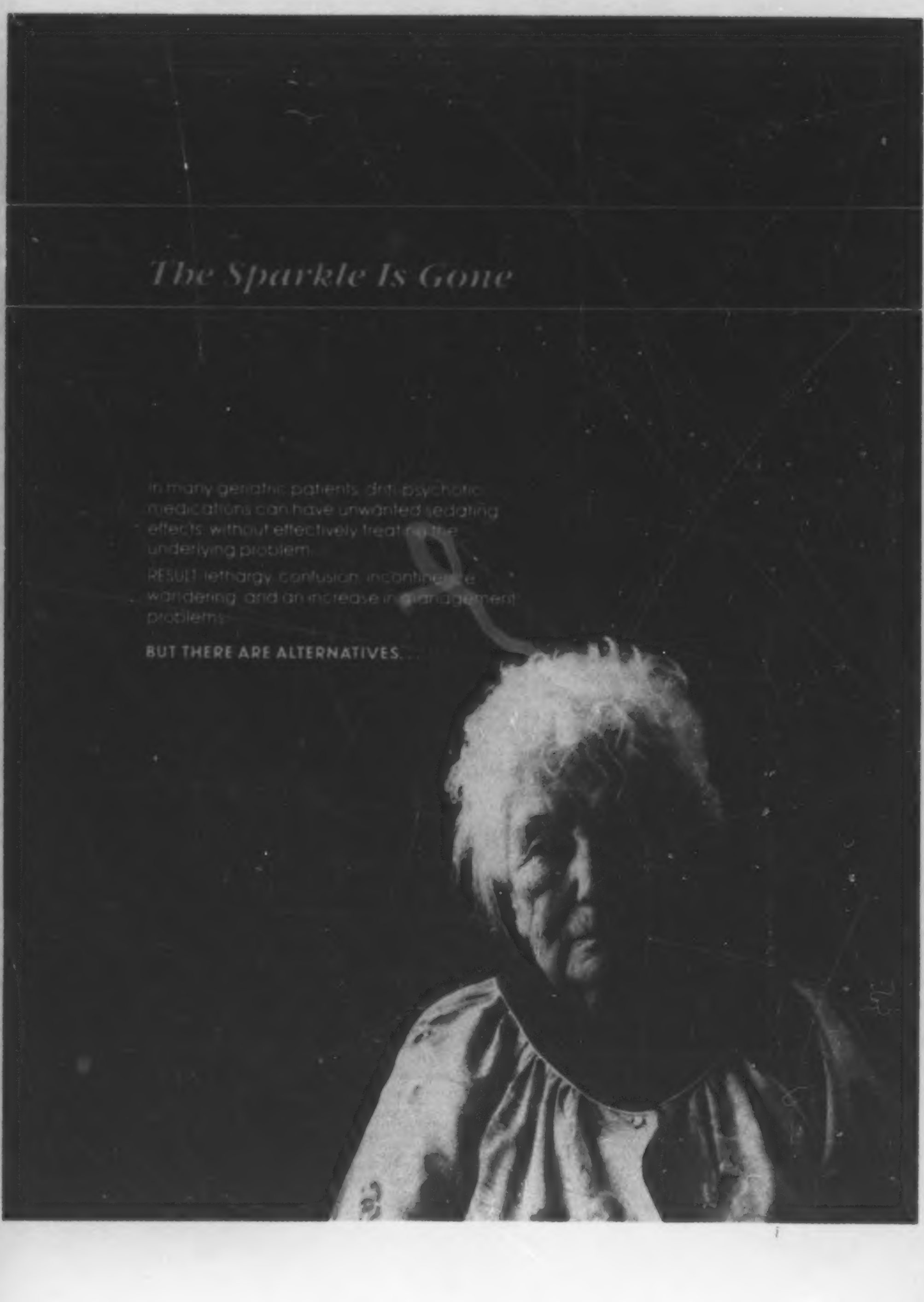


The Sparkle Is Gone

In many geriatric patients, anti-psychotic medications can have unwanted sedating effects, without effectively treating the underlying problem.

RESULT: lethargy, confusion, incontinence, wandering, and an increase in management problems.

BUT THERE ARE ALTERNATIVES....

Personal contact may be more effective than drugs.

Demented patients may become agitated because of frustration at their inability to express their needs. Nursing interventions may work better than medications in calming the agitated patient.[1]

Medical history and physical examination may uncover a treatable cause of agitation.

Some medical conditions can cause agitation: hypoxia, thyroid disease, acute myocardial infarction, drug therapy,[2] and many others. These may require specific diagnosis and treatment.

—offer fluids

—check caloric intake

—encourage participation in activities

—increase ambulation and exercise

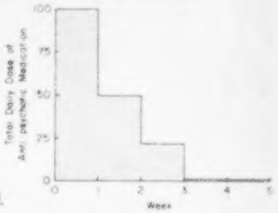
—reassure and change environment

—an analgesic may be indicated

—alter toileting routine; evaluate incontinence

—increase fiber, fluids; soften stools

Some patients need more stimulation and others need less. Some residents feel more secure in quiet environments, while others enjoy interaction with other people. Loud voices frighten some residents while others feel safer with noise. As much as possible, it's important to individualize the environment for each patient.



anti-psychotic medications from non-psychotic patients currently receiving them. Many will do equally well, or better, off drugs.[3,4]

whenever possible establish the patient's behavior pattern over several days. Many behavior problems are short-lived and will resolve on their own, without sedation.

in the patient with severe behavior disorders when other interventions have failed.

- **Before starting an anti-psychotic drug, identify the specific target behavior to be treated and define the goals of therapy;**
- **Use the lowest possible doses;**
- **Prescribe short courses;**
- **Monitor closely for side-effects in all patients receiving these drugs.[5]**

Withdrawing medications, personal contact, looking for treatable conditions, and environmental changes may take some extra time at first. But in the long run, these approaches will benefit both residents and staff as the side effects of unnecessary anti-psychotic drugs diminish.

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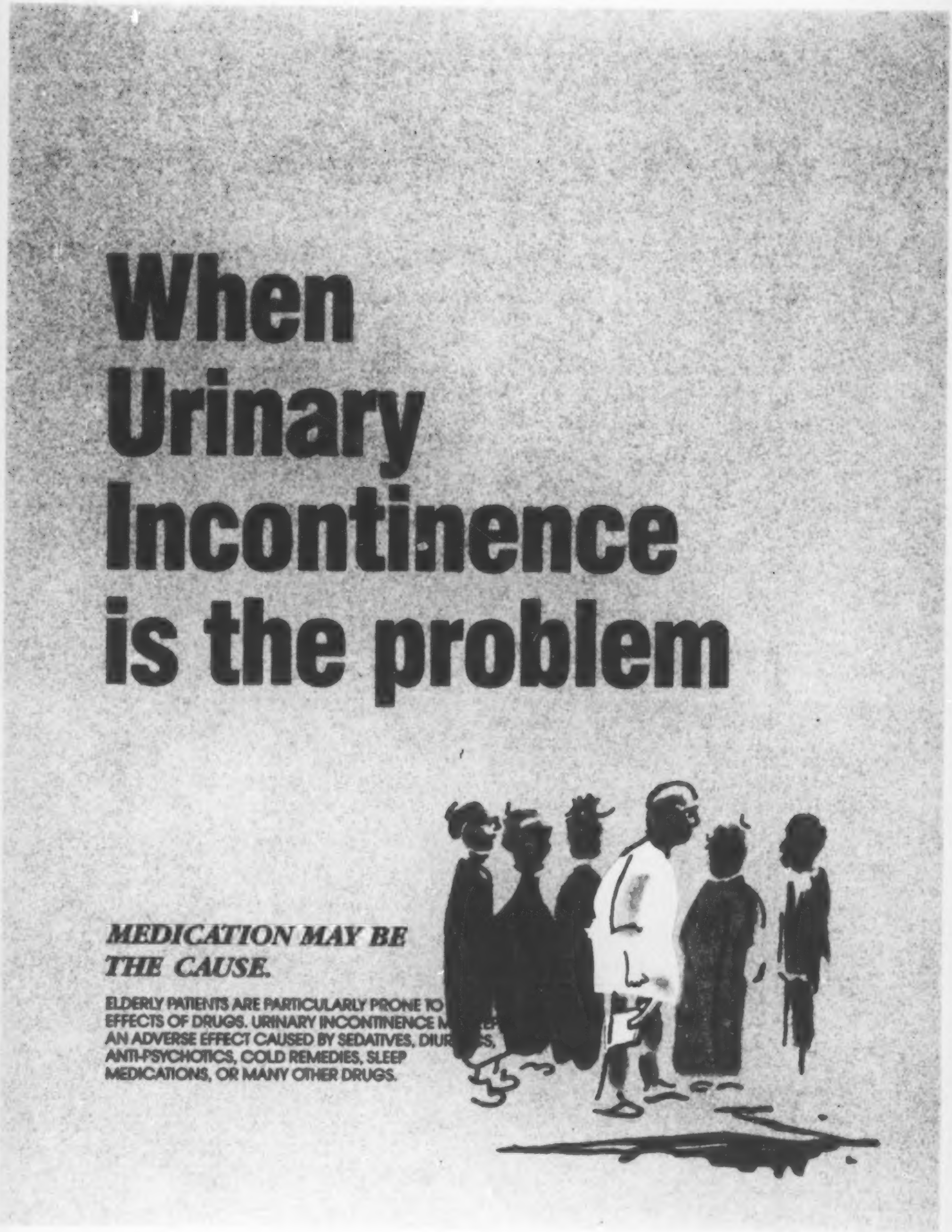

When Urinary Incontinence is the problem

MEDICATION MAY BE THE CAUSE.

ELDERLY PATIENTS ARE PARTICULARLY PRONE TO [illegible] EFFECTS OF DRUGS. URINARY INCONTINENCE M[illegible] AN ADVERSE EFFECT CAUSED BY SEDATIVES, DIUR[illegible]S, ANTI-PSYCHOTICS, COLD REMEDIES, SLEEP MEDICATIONS, OR MANY OTHER DRUGS.

INCONTINENCE IS NOT A NORMAL PART OF AGING.[1] Yet it is one of the most common problems affecting nursing home patients.[2] Incontinence can lead to poor self-image, skin breakdown, infection, and falls.[3] Caring for these patients also places an extra burden on staff . . . a burden that can often be prevented.

IN AN ELDERLY PATIENT, DRUGS CAN LEAD TO INCONTINENCE IN SEVERAL WAYS. Anticholinergic drugs such as antihistamines, many anti-psychotics, and some antidepressants can cause urinary retention. This in turn may lead to overflow incontinence.[4] Diuretics, especially when given late in the day, may overwhelm the older person's bladder capacity.[5] Sedatives can cloud the mental status and can cause patients to lose bladder control.[6]

MEDICATION REVIEW ALONE MAY INDICATE THE CAUSE OF INCONTINENCE.[1] *Stopping or changing a drug may cure the problem.* A patient with normal bladder function is more comfortable, is safer, is more functional, and is easier to care for.

SOME DRUGS THAT CAN CAUSE INCONTINENCE

ANTI-PSYCHOTICS	
chlorpromazine (Thorazine) →	ANTICHOLINERGIC & SEDATING
thioridazine (Mellaril) →	
thiothixine (Navane) →	
haloperidol (Haldol) →	

ANTIDEPRESSANTS	
amitriptyline (Elavil) →	THE MOST ANTI-CHOLINERGIC & SEDATING ANTI-DEPRESSANTS
doxepin (Sinequan, Adapin) →	

ANTIHISTAMINES	
diphenhydramine (Benadryl) →	VERY ANTI-CHOLINERGIC & SEDATING MAY ALSO BE ALPHA-BLOCKERS
hydroxyzine (Atarax) →	
cold remedies →	

DIURETICS	
furosemide (Lasix) →	MAY OVERWHELM THE OLDER PERSON'S ABILITY TO TOILET
bumetanide (Bumex) →	
ethacrynic acid (Edecrin) →	

ANTIHYPERTENSIVES	
eg. methyldopa (Aldomet), →	AFFECT ALPHA RECEPTORS IN AUTONOMIC NERVOUS SYSTEM
clonidine (Catapres), →	
prazosin (Minipress), →	
guanethidine (Ismelin) and reserpine →	

FOR ALL INCONTINENT PATIENTS:

- **CONSIDER MEDICATION AS A POSSIBLE CAUSE**
- **REVIEW ENTIRE DRUG REGIMEN**
- **STOP OR CHANGE MEDICATIONS THAT MAY LEAD TO INCONTINENCE**
- **CONSIDER FURTHER EVALUATION IF SYMPTOMS PERSIST**

"NOW THAT MRS. SMITH IS ON FEWER MEDICINES AND IS DRY, SHE'S MUCH BETTER OFF."

"YES, AND SO ARE WE!"

REFERENCES: 1. Resnick N. Yalla S. Management of urinary incontinence in the elderly. New England Journal of Medicine 1985; 313:800-804. 2. Krane R, Siroky M. Diagnosis and treatment of urinary incontinence. Annual Review of Geriatrics 1982; 2:385-402. 3. Ebersole P, Hess P. Towards Healthy Aging. St. Louis, MO: CV Mosby; 1985; pg. 219. 4. Resnick N. Urinary incontinence in the elderly. Medical Grand Rounds 1984; 3(3):281-290. 5. Willington FL. Urinary incontinence and the significance of nocturia and frequency. In: Cape R, ed. Fundamentals of Geriatric Medicine. New York, NY: Raven Press, 1983; pp. 117-127. 6. Williams M, Pannel F. Urinary incontinence in the elderly. Annals of Internal Medicine 1982; 97:895-907.

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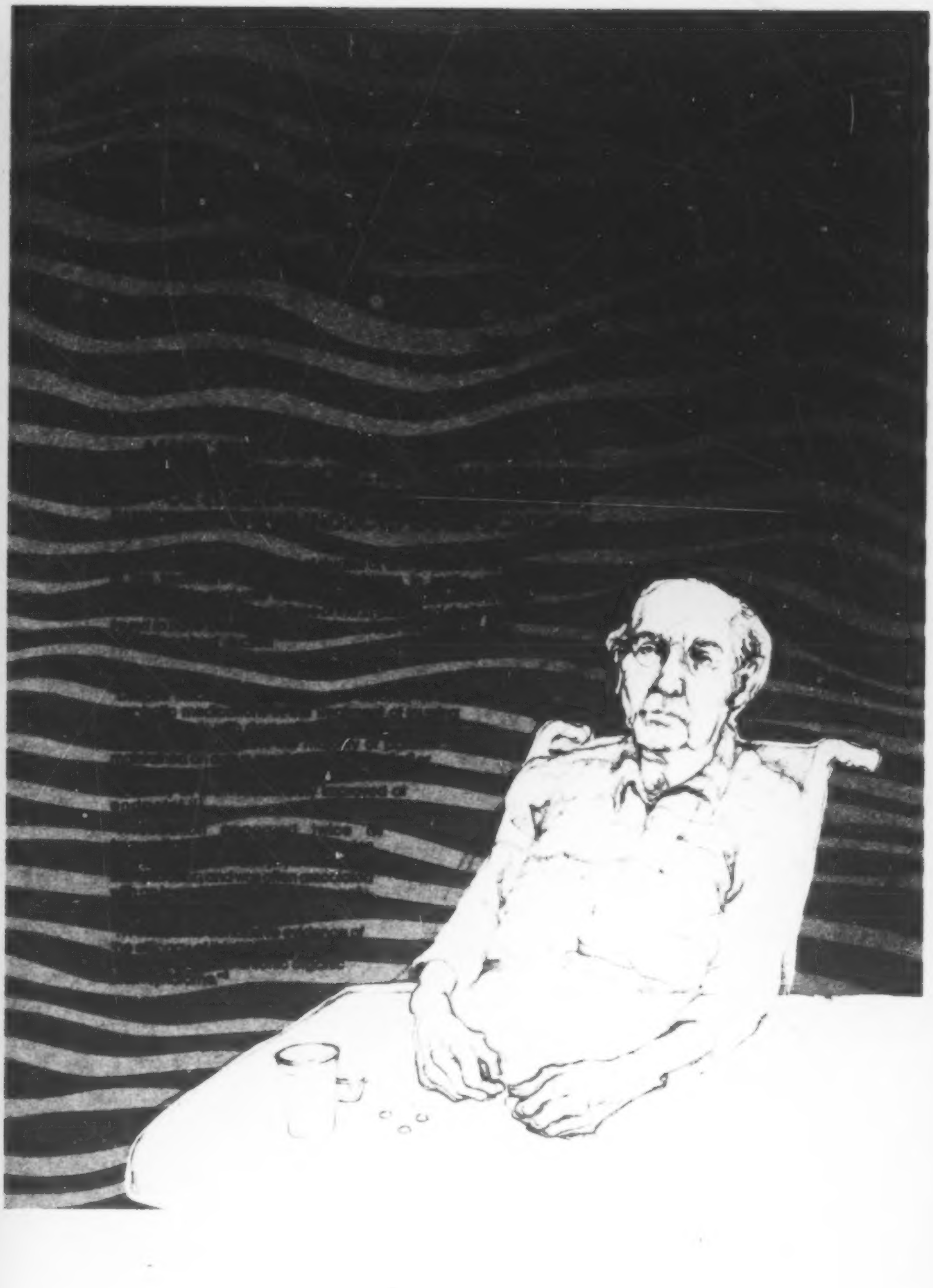

COMMONLY USED ANTI-PSYCHOTIC DRUGS:

haloperidol (Haldol)
thioridazine (Mellaril)
chlorpromazine (Thorazine)
thiothixene (Navane)
fluphenazine (Prolixin)
mesoridazine (Serentil)
trifluoperazine (Stelazine)

THESE DRUGS ARE VERY EFFECTIVE IN PRODUCING ADVERSE REACTIONS IN THE ELDERLY

- **PARKINSONIAN SYMPTOMS (Extra-pyramidal signs):**[6]
  All the classical signs and symptoms of Parkinson's Disease can be mimicked by anti-psychotic drug side-effects. These include stiffness, tremor, difficulty swallowing and walking, and loss of facial expression. Worst offenders: Haldol, Prolixin, Navane, Stelazine.
- **TARDIVE DYSKINESIA:**[7]
  Involuntary twitching of the lips, tongue, or other parts of the body. There is no clear evidence that any anti-psychotic drug is safer than any other in preventing this potentially disabling condition. Stopping the drug *may* cause the symptoms to cease, but it may also worsen them or leave them unchanged. The elderly are more likely than any other group to develop tardive dyskinesia from use of these drugs. Tardive dyskinesia can be permanent.
- **AKATHISIA:**[6]
  An uncontrollable need to move around, change position, to stand up, and to pace. This is actually a *result* of too much anti-psychotic medication, but it is often mistaken for a sign that the patient is still agitated, leading to even more drugs being given.[8] In fact, a patient with these symptoms needs a trial of *less* drug, or none at all, to clear up the problem.
- **ORTHOSTATIC HYPOTENSION:**[5]
  Many of these drugs cause blood pressure to drop upon standing, and may lead to falls and fractures. Worst offenders: Thorazine, Mellaril.
- **OVERSEDATION:**[9]
  Often, all these drugs do is sedate, and the elderly are particularly prone to oversedation. This can mimic depression or senile dementia, but is easily reversible when the offending drug is stopped. Worst offenders: Mellaril, Thorazine.

RECOMMENDATION: Plan a trial of tapering anti-psychotic drugs for geriatric patients now receiving them. Reduce dosage by up to 50% each week until the patient is off the medication, or presents symptoms demonstrating that the drug is required.

Usually, the taper will be uneventful, and may even result in clinical improvement.

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Senator **Simpson**. I come from a personal situation where those things are very real.

And so, now, I believe Dr. Simonson is next. Please share your testimony, sir.

STATEMENT OF WILLIAM SIMONSON, PHARM.D., ASSOCIATE PROFESSOR OF PHARMACY, COLLEGE OF PHARMACY, OREGON STATE UNIVERSITY

Dr. **Simonson**. Thank you, Senator.

I would like to thank the committee for the invitation to speak today. I would also like to commend Surgeon General Koop for his recently completed workshop on health promotion and aging. There are some very positive comments that have come out of that workshop that I think would address some of the issues that we are discussing today.

I would like to give a couple of comments about adverse reactions—specifically about labeling of drug information—and give some positive interventions that I think can help solve some of the problems that we have discussed.

In my opinion the biggest problem of adverse drug reactions is not the adverse reaction itself, although that can be very tragic, as we've heard today. But the biggest problem, rather, is that many adverse drug reactions go unnoticed.

I think many health professionals have a mistaken attitude that aging is synonymous with a stereotype that I call the unfair elderly stereotype, that of confusion, forgetfulness, lethargy, constipation, urinary retention—a number of negative terms. It certainly is not synonymous with aging and, in fact, really discriminates against the majority of elderly individuals who have none of those traits.

When many of those stereotypes are adopted by health professionals it is sometimes the case where an adverse drug reaction occurs and it is not noticed. Indeed, it is very difficult to differentiate between symptoms of a disease and manifestations of adverse drug reactions.

But if there is a misdiagnosis, we often get into a vicious cycle which is called polypharmacy, or I think more appropriately called polymedicine, which is analogous to a dog chasing its tail. Where we are treating an adverse drug reaction with another drug. That causes another adverse reaction and we add another drug. The best intervention in that case would have been not to start the therapy in the first place, or to evaluate the therapy at some point and try to discontinue any inappropriate medication.

I often wonder how many elderly patients have been sentenced to a life of institutionalization with chemical restraint because they experience confusion or psychosis because of an adverse drug reaction and were put on psychotropics and never really knew what happened.

I wonder how many of these patients were actually unaware of the problem, themselves. I think that this is the most tragic outcome of adverse drug reactions.

I hope it doesn't occur often, but I am afraid it probably occurs more often than we would like to believe.

Regarding geriatric labeling: in the last decade we have really gained quite a bit of information regarding the adverse effects of medications and the pharmacokinetics and pharmacodynamic alterations that occur in the elderly.

But in spite of these gains, the detailed and clinically usable information—that's, perhaps, the key: clinically usable information—has not really been disseminated.

I have an ongoing study of the Physician's Desk Reference, and in 1982, for example, the specific geriatric dosage was only listed for 17 of the top 200 most commonly prescribed medications. And a specific note on adverse drug reactions was only provided in 18 of these top 200 medications. It really is not much improved today.

In close scrutiny of current product labeling of 24 of the most commonly used medications in the elderly, as Senator Heinz pointed out earlier, only 3 of these medications mention the geriatric patient under adverse drug reactions; and only 5 mention a specific geriatric statement under dosage.

Specific geriatric labeling for all products commonly used by the elderly is desirable and it is feasible. This labeling could define a specific geriatric dosage, or it could refer to a more general precaution.

For example, the USPDI—Drug Information for the Health Care Professional—is an annual publication of the U.S. Pharmacopeial Field Convention. This reference routinely provides geriatric precautions to consider.

For example, the following statement appears in the 1988 USPDI for the drug category "benzodiazepines," which are drugs used to reduce anxiety and to induce sleep. "Precautions to consider. Geriatrics: geriatric patients are usually more sensitive to the central nervous system effects of benzodiazepines. Parenteral administration of benzodiazepines may be more likely to cause apnea, hypotension, bradycardia, or cardiac arrest in geriatric patients."

This publication also provides specific geriatric doses for 11 of the 12 approved benzodiazepine compounds, as well as a detailed statement on proper dosing, which is included in my written testimony.

The availability of more complete geriatric labeling alone will not be enough to guarantee proper prescribing. For example, three sleeping medications commonly used in the elderly, Dalmane, Restoril, and Halcion, have specific geriatric dosage recommendations of 15 milligrams, 15 milligrams, and 0.125 milligrams, respectively. Yet, it is common for prescribers to write for the dosage that is more appropriate for younger adults. Ironically, this occurs in spite of the fact that the doses have been stressed by manufacturers to be the geriatric doses for these products.

So simply the availability of the information is not enough.

I have just a few suggestions in conclusion regarding potential positive interventions to solve some of these problems.

First, existing FDA labeling requirements are inadequate in regards to geriatric-specific information. Labeling requirements should include a specific statement on the likelihood of adverse drug reactions occurring in elderly patients.

In addition, specific geriatric dosage requirements should be prominently noted when available, and if not available, a general statement on potential alterations in dosage requirements should be required.

Second, the FDA should also require that adequate geriatric studies be performed prior to the approval of any new drug to determine the valuable pharmacokinetic and pharmacodynamic information about that drug. This information would help to determine if a specific geriatric dosage would be necessary.

Third, postmarketing surveillance should be required to observe large populations of elderly consumers of medications. In this way the occurrence of adverse drug reactions could be noticed as soon as possible after a drug is marketed. The early discovery of such problems would aid in the development of appropriate intervention, such as dosage alteration, so that the problem could be reduced or eliminated.

Fourth, existing information on geriatric precautions and dosage requirements could be disseminated to prescribers by, for example, condensing information that already exists in the USPDI—perhaps in a little booklet or pamphlet.

With adequate funding it might be possible to collate this information and disseminate it more widely to the people who need it.

And, finally, centers for geriatric pharmacology and pharmacy, as well as nursing home pharmacology and pharmacy, should be established with the support of the pharmaceutical industry.

These centers would be responsible for conducting the research on the effects of drug therapy in the elderly, and they could also investigate new practice roles for health professionals working with the elderly to encourage the appropriate use of medications in this segment of the population.

Again, thank you, Senator.

[The prepared statement of Dr. Simonson follows:]

TESTIMONY

of

WILLIAM SIMONSON, PHARM.D.

before the

UNITED STATES SENATE SPECIAL COMMITTEE ON AGING

SENATOR JOHN MELCHER, CHAIRMAN

on

"ADVERSE DRUG REACTIONS: ARE SAFEGUARDS ADEQUATE FOR THE ELDERLY?"

DIRKSEN SENATE OFFICE BUILDING

ROOM 628

MARCH 25, 1988

Thank you Senator Melcher for providing me with this opportunity to address your committee. I am an Associate Professor of Pharmacy at Oregon State University and a clinical pharmacist with 20 years of experience in the area of geriatrics. Adverse drug reactions are a major problem associated with drug therapy in the elderly however I believe that steps can be taken to significantly reduce their occurrence and negative impact.

INCREASED INCIDENCE OF ADVERSE DRUG REACTIONS IN THE ELDERLY

Elderly consumers of medications are more likely to experience adverse drug reactions for a number of reasons. Various changes in body composition and physiologic functions that are associated with the aging process can have a significant effect on the clearance of medications from the bloodstream. These changes often result in a decreased drug clearance in the elderly and a corresponding increase in likelihood of adverse reactions. Many of these adverse effects are predictable if adequate information on the pharmacokinetics and pharmacodynamics of a medication is available. The elderly are also more likely to experience idiosyncratic adverse drug reactions where the adverse effect is apparently unrelated to the expected effect of a medication. An example of this type of adverse reaction is when a patient experiences excitation and agitation instead of the expected sedation after taking a medication for sleep.

Another reason for the increased incidence of adverse drug reactions in the elderly is the fact that, as a group, the elderly consume more medication than younger patients. While the elderly in the United States make up approximately 12 percent of our total population this same segment purchases approximately 25 to 30 percent of all prescription and non-prescription medications used.

In addition to this higher rate of consumption, the types of medications consumed by the elderly are often inherently more toxic. The medications that they commonly use for their serious cardiac, circulatory, and neurologic conditions are often quite effective but are also powerful and potentially dangerous.

THE CONSEQUENCES OF ADVERSE DRUG REACTIONS

In my opinion the biggest problem caused by adverse drug reactions in the elderly is not the adverse reaction itself, although the outcomes can be tragic, but rather the fact that these adverse reactions often go unnoticed. Many health professionals have a mistaken attitude about the elderly patient that perpetuates what I refer to as "the unfair elderly stereotype". This stereotype of confusion, depression, anorexia, weakness, lethargy, ataxia, forgetfulness, tremor, constipation. diarrhea, and urinary retention unfairly discriminates against the majority of elderly individuals who manifest none of these characteristics. Since the most common manifestations of adverse drug reactions in the elderly are precisely the same symptoms of this unfair stereotype, professionals who believe that aging is synonymous with deterioration of physical and mental function often overlook medications as the cause of their patient's deterioration. Indeed it is often difficult to differentiate between the symptoms of a disease and the manifestations of adverse drug reactions, however if an adverse reaction is misdiagnosed the vicious cycle often referred to as polypharmacy, but I believe more appropriately called polymedicine, is begun. In this scenario, which is analogous to a dog chasing its tail, more and more medications are used to treat the symptoms and toxicities that are being caused by unnecessary drug therapy. Still more unnecessary drugs are added rather than discontinuing the offending agent or agents, which would have been the most appropriate intervention in the first place. I often wonder how many elderly patients have been sentenced to a life of institutionalized chemical restraint simply because they experienced adverse drug reactions manifested as confusion, or psychosis. I wonder how many of these patients, who were probably themselves unaware of the actual cause of their problems, have been tranquillized with powerful anti-psychotic agents, institutionalized, and condemned to an over-drugged demise. This is the most tragic outcome of adverse drug reactions because it is preventable. One can only guess how often this has occurred. Not often I hope, however I believe that this scenario has probably occurred more often then we would like to imagine.

GERIATRIC LABELING

In the last decade a considerable amount of knowledge has been gained regarding the types of pharmacokinetic and pharmacodynamic alterations that commonly occur in the elderly. In spite of these gains detailed and clinically usable information is still unavailable for most drug products. For example, scrutiny of the available product labeling in 1982 revealed that a specific geriatric dosage was available for only 17 of the 200 most commonly prescribed medications and a specific note on adverse reactions was provided in only 18 of the top 200. It is not much improved today.

In scrutiny of the current product labeling of twenty four of the most commonly used medications in the elderly only three mention the geriatric patient under ADVERSE REACTIONS while only five geriatric mentions are found under DOSAGE AND ADMINISTRATION.

Specific geriatric labeling for all products commonly used by the elderly is desirable and feasible. This labeling could define a specific geriatric dosage or it could refer to more general precautions. For example the USPDI, DRUG INFORMATION FOR THE HEALTH CARE PROFESSIONAL, routinely provides geriatric precautions to consider. The following statement appears in the 1988 USPDI for the drug category "benzodiazepines" which are drugs that are used to reduce anxiety and induce sleep.

> PRECAUTIONS TO CONSIDER
>
> GERIATRICS: Geriatric patients are usually more sensitive to the CNS effects of benzodiazepines.
> Parenteral administration of benzodiazepines may be more likely to cause apnea. hypotension, bradycardia, or cardiac arrest in geriatric patients.

The publication also provides specific geriatric dosages for eleven of the twelve approved benzodiazepine preparations as well as the following statement on proper dosing:

> **GENERAL DOSING INFORMATION**
>
> **Geriatric or debilitated patients, children, or patients with hepatic or renal function impairment or low serum albumin should receive decreased initial dosage since elimination of benzodiazepines, especially the long half-life ones, may be decreased in these patients, resulting in increased CNS side effects such as over-sedation, dizziness, or impaired coordination.**
> **Benzodiazepines may suppress respiration, especially in the elderly, the very ill, the very young, and those patients with limited pulmonary reserve. Lower doses may be required for these patients.**

The availability of more complete geriatric labeling alone will not be enough to guarantee proper prescribing. For example three sleeping medications used commonly in the elderly; Dalmane, Restoril, and Halcion have specific geriatric dosage recommendations of 15mg,15mg and 0.125mg respectively, yet it is common for prescribers to write for the dosage most appropriate for younger adults. Ironically this occurs in spite of the fact that the geriatric dosages for these products are stressed heavily in each manufacturer's promotional literature. Interestingly the manufacturer of Dalmane was one of the first medications to specify a geriatric dosage in addition to its standard adult dosage and they continue to do so yet prescribers often fail to specify the geriatric dose. The availability of geriatric-specific labeling such as this is important however its mere existence does not guarantee its use. This information must be printed in references that are routinely read by prescribers, such as the Physician's Desk Reference (PDR), and must be reinforced through other references and promotional material.

THE ROLE OF THE PHARMACEUTICAL INDUSTRY

Pharmaceutical manufacturers are limited by regulation as to what they can include in the labeling of a product. Since the clinical experience with most drugs is quite limited when the product's labeling is being developed, there is naturally a paucity of geriatric specific information.

Additionally most drug testing is performed in healthy younger adults, even though the product may be approved and marketed for a condition that is common in the elderly.

While many problems exist with the use and misuse of medications in the elderly population the pharmaceutical industry appears to have a sincere interest in arriving at solutions that promote the safety and enhance the efficacy of medication use in elderly patients. An example of the efforts of the industry is demonstrated by a recent report issued by the Pharmaceutical Manufacturers Association entitled "New Research & New Concerns: Pharmaceuticals for the Elderly". This report reaffirms the belief that adverse drug reactions are the result of a multitude of factors including inappropriate prescribing by physicians, age-related physiological changes and poor patient compliance. The report recommends a number of positive interventions including the establishment of centers for geriatric pharmacology and pharmacy as well as centers for nursing home pharmacology and pharmacy. It also recommends a committed research effort to address and solve the many problems that are associated with the use and misuse of medications by the elderly. In my opinion these would be positive and productive steps. It is also my opinion that the pharmaceutical industry should provide the funding that would be required to develop these centers. This would be only logical since the information gained from these centers would ultimately lead to more effective use of medications in the elderly while at the same time increasing pharmaceutical sales to this rapidly growing segment of the population.

Since the elderly are responsible for a large share of pharmaceutical sales it should not come as a surprise that the industry supports and encourages research and education in this area. Indeed it is in the manufacturers best interest since any advancements in this area can result in increased sales opportunities. An example of the potential impact of the geriatric prescription drug market was recently pointed out to me by a representative of a major pharmaceutical company. After studying the sales of his company it was determined that approximately 70 percent of his companies sales were consumed by patients age 55 or older!

SUGGESTIONS AND POTENTIAL POSITIVE INTERVENTIONS

Existing FDA labeling requirements are inadequate in regards to geriatric specific information. Labeling requirements should include a specific statement of the likelihood of adverse drug reactions occurring in elderly patients. In addition, specific geriatric dosage requirements should be prominently noted when available and if not available a general statement on potential alterations in dosage requirements should be required.

The FDA should also require that adequate geriatric studies be performed prior to approval of any new drug to determine valuable pharmacokinetic and pharmacodynamic information about the drug. This information would help determine if a specific geriatric dosage would be necessary.

Post marketing surveillance should be required to observe large populations of elderly consumers of medications. In this way the occurrence of adverse drug reactions could be noticed as soon as possible after a drug product is marketed. The early discovery of such problems would aid in the development of appropriate interventions such as dosage alterations so that the problem could be reduced or eliminated. Existing information on geriatric precautions and dosage requirements could be disseminated to prescribers by condensing information that is already available in the USPDI. With adequate funding it would be possible to collate this geriatric-specific information and distribute it to health professionals.

Centers for geriatric pharmacology and pharmacy as well as nursing home pharmacology and pharmacy should be established with the support of the pharmaceutical industry. These centers would be responsible for conducting the research on the effects of drug therapy in the elderly and could investigate new practice roles for health professionals working with the elderly to encourage the appropriate use of medications in this segment of the population.

CONCLUSION

In conclusion, I would again like to thank the committee for this opportunity to present my views on the crucial topic of adverse drug reactions in the elderly. I have reviewed some of the reasons for the occurrence of these adverse reactions and have shared some of my experiences and observations. I have also presented some suggestions that, in my opinion, would have a substantial impact on the reduction of adverse reactions in this portion of the population. I hope that some of these suggestions can become a reality.

Senator SIMPSON. Thank you all. That was very provocative, fascinating material. It is obviously a complex issue for us, for the chairman, and all of us.

The elderly, as you indicate, take more prescriptions, but they have more need for that. The confusion—that's a disturbing thing, as you point out, how they could get into the cycle and never know they got into the cycle of the dependency, or the reaction, or both.

I won't go back and tell local war stories, but I remember, too, how many people that I dealt with in the practice—elderly people—were taking Valium. I would go to the drug store and get that little sheet of paper on valium from the Pharmacological Digest, which fills more space than any other drug in that volume as to the side effects, contra-indications of that particular drug, I guess. The elderly would always be surprised and irritated when I would share with them that information.

So we have to look at the whole issue of quality in geriatric medicine, obviously.

Let me ask you this. We have focused here—and rightly so—on overprescribing and some of the dramatic effects that produces. Is there any concern with underprescribing and patient compliance where elderly persons, because of things you have described and the way they are described, say, "Well, that's just old age. Don't give them anything?" So where are we there, where they would not be getting life-saving drugs? That would be of interest to me.

Dr. AVORN. That's a very prevalent problem, as well. One good example is high blood pressure. In the last couple of years very good data have been pulled together showing that treating high blood pressure in the elderly is definitely worth doing, although there are a lot of physicians out there who seem to have the feeling that if you make it past 65 and you've got high blood pressure, well, treating it is probably going to cause more trouble than it is worth.

Yet we now have very good evidence that you can prevent cardiovascular disease by treating high blood pressure in the elderly.

That is one example of a condition that could be treated more, but there is underprescribing.

Similarly, I think you are right that patients sometimes have a sense that, "I'm taking all these pills. How can I know if they are all necessary? Probably some of them aren't, so I just won't take them all."

That is really another result of haphazard prescribing, because the ones that they skip may be the really life-saving ones, and the ones that they take may not be the most important for them. So, yes, that is a problem.

Dr. SIMONSON. Yes, Senator, it is important to underscore that I think all of our comments are not anti-drug, per se, but they are anti-inappropriate drug use. The trends have been for excessive use. But many of the medications that are on the market now and that are coming out in the next few years are remarkably effective. So not only can drugs increase the quality of life, they can make health care less expensive and make people happier and healthier.

The inappropriate use is what we are really trying to eliminate.

Senator SIMPSON. Do you have anything to share?

Dr. Colinger. Well, in the setting of private practice it is part of the physician's responsibility to advise people of possible drug side effects. In particular, blood pressure medication is notorious for making people feel bad.

So I try—at least in my own practice—to educate them about what may happen. I advise them, though, that if it does they are to call me, not just to quit.

As an on-going thing, their medications are routinely reviewed. The human doesn't stay static. Age does make a difference. What was true when you were 40 is not necessarily true when you are 80. It requires some diligence on the part of the practitioners in the nation to make sure that we can minimize side effects.

Senator Simpson. What about research into this problem? You have identified research. As Ms. Henry states, it is in those homes. It is difficult to always find those things.

With the tremendous advances in modern medicine isn't there really kind of an information gap?

Dr. Avorn. Very definitely. The best available information that is in existence in medical schools around the country is in many ways not translated to the practicing doctor.

Dr. Colinger is a very impressive example of where that can work. But, unfortunately, that often does not occur.

Senator Simpson. Our chairman has returned. Thank you, Mr. Chairman. It was a very interesting panel. A very finely balanced group. I thank you. I think it has been an excellent hearing.

The Chairman. Thank you very much, Senator Simpson.

Dr. Colinger, what is your specialty?

Dr. Colinger. I am a family practitioner.

The Chairman. How can we best spread the word that the elderly have special problems with medications.

Dr. Colinger. I think first of all you need a recognition that there is a problem. We are trained—unfortunately, sometimes—to intervene with medications. That is not necessarily the appropriate approach for certain types of problems.

The example would be the nursing home resident that becomes a little bit unruly. So what? If they are unruly, they are unruly. But why intervene with a potentially lethal medication?

At least in our facility we try to look at the quality of life that we are providing for that patient and we think that paramount.

There are some reasons to do it. If an individual is in danger to themselves or endangering other patients in the facility, then we have to act. But beyond that, there is no reason to act.

So I think there is a big problem with overprescribing the medications.

The Chairman. You mentioned in your testimony that as a physician you would not resent a Federal program that would look at the number of drugs that were prescribed for patients and the type of drugs that were prescribed for elderly patients. I assume you meant some sort of screening and evaluation by Medicare and Medicaid; is that right?

Dr. Colinger. Yes, sir. That is what I meant.

The Chairman. I wonder if that's—maybe that is possible. At least it would be on a random basis—spot check—as all this stuff gets on computers.

Dr. COLINGER. One of my colleagues just mentioned that with the computer systems that are available, the linkage that is available, the drug profiles for a particular individual may be available to the carriers that pay for the medications. In that way you are going to know who is taking what and for what reasons. If you come to a conclusion that a certain physician is overprescribing, I think there needs to be some intervention.

The CHAIRMAN. Doctor Simonson, you published a book, "Medication and the Elderly." Could you—maybe you've already mentioned, or somebody has asked you, but when was the publication date?

Dr. SIMONSON. In 1984.

The CHAIRMAN. In 1984? It is fairly recent, then.

In your survey of 432 pharmacists, were those pharmacists across the country?

Dr. SIMONSON. These were pharmacists that work in some type of geriatric practice across the United States—either nursing home or hospital—but they specialized with the elderly patient.

The CHAIRMAN. Were the 432 pharmacists surveyed involved in nursing homes?

Dr. SIMONSON. Were working primarily—they had some identification as a pharmacist with an interest in geriatrics.

The CHAIRMAN. So a lot of them would be in a nursing home?

Dr. SIMONSON. Yes.

The CHAIRMAN. Did 29 percent of them—is that a correct figure—cite that they felt that they had inadequate professional skills.

Dr. SIMONSON. The study that you are referring to was the study looking at pharmacists' perceptions of the biggest problems in geriatric pharmacy practice. The number one problem that they identified was inadequate knowledge of the scientific or pharmacologic information regarding the elderly patient.

I did another survey—if I can just interject, Senator—that we tried to assess undergraduate training and the effect of geriatric knowledge and pharmacists, and we found that 25 percent of pharmacists felt that their undergraduate training did not prepare them well for geriatrics. Another 55 percent felt that they prepared them only slightly well.

So about 80 percent of the pharmacists that we surveyed felt that they did not have sufficient training in geriatrics. It is much like medicine. Pharmacy schools and medical schools have similar problems.

The CHAIRMAN. Every pharmacist must have continuing education to retain their license; do they not?

Dr. SIMONSON. Most States require continuing education, but I believe there are a few States that do not.

The CHAIRMAN. But in every State that requires continuing education, the question of prescription drugs in terms of geriatrics could be brought immediately to their attention—I mean within a year's time.

Dr. SIMONSON. Absolutely.

The CHAIRMAN. Is that true?

Dr. SIMONSON. Yes. Many programs do concentrate on geriatrics. There are quite a few continuing education programs now in the area of geriatrics responding to my surveys and other needs. Pharmacists have a great interest in geriatrics, and they have a desire to learn more.

The **Chairman**. Well, would each of you—I'm asking physicians what they think pharmacists ought to do, but I'll ask it anyway: Would each of you feel that that ought to be required? I mean required; federally required.

Dr. **Simonson**. Geriatric training?

The **Chairman**. Well, we have to deal with life as it is. If there are all the licensed pharmacists out there, I mean requiring in their continuing education that some of it be in geriatrics.

Dr. **Simonson**. If a pharmacist is practicing in a pediatric clinic there is no need for geriatric knowledge, but very few pharmacists are in that area. I think geriatrics should be required both in the undergraduate program and on a post-graduate basis. Absolutely.

The **Chairman**. How is this post-graduate information shared?

Dr. **Simonson**. Continuing education.

The **Chairman**. Continuing education. Well, it's probably not necessary in a pharmacist only dealing with youngsters that never deals with the elderly. But almost every pharmacist in the Giant store—that's a food chain here—or Drug Fair, or whatever, is going to be filling prescriptions for the elderly; is he not?

Dr. **Simonson**. Absolutely.

The **Chairman**. Well, I think our national figures show that. About 30 percent of the prescription drugs are used by the elderly.

Do you feel the same on that, Dr. Avorn?

Dr. **Avorn**. Yes, I do. But I think that it is really my profession more than Dr. Simonson's that is the cause of the problem.

The **Chairman**. Oh. We're going to get to you.

Dr. **Avorn**. OK. But if we are sticking with pharmacy: yes, I think there ought to be mandatory continuing education. But I would even take it one step further. Many of the health professions have requirements on paper that people show that they have taken *x* number of courses, and that they've signed up, and turned up somewhere. I don't think that is adequate because what it basically means is that you have paid your registration fee, you checked into the hotel (which may be in Miami Beach), and then you went home again.

The **Chairman**. Nobody gives you a test, do they?

Dr. **Avorn**. No. And what we really need to move toward is some demand not just that one turns up at a course, but that one actually learns something.

One way of implementing that is that there be some requirement that physicians and pharmacists demonstrate competency. This could be required every 5 or 10 years. It can be a baseline minimal level of competency: Not just that you paid your money and went to a course in some pleasant climate, but that, indeed, you learn something and know how to practice.

If you don't know that, I think we should ask whether taxpayer money should be paid reimbursing physicians or pharmacists for services if they can't demonstrate competency in this area.

The **Chairman**. Dr. Colinger.

Dr. **Colinger**. I would not disagree with what has been stated, but I don't think that it is going to solve the problem. Education is fine. You can require that people have so many CME credits; but it is what you do with the information that is the crux of the problem.

As I see it, until you really establish some way of correcting prescribing patterns that physicians do, you are not going to get to the crux of the matter.

If a particular physician has attended whatever continuing medical education course there is, but he still has a tendency to put people on benzodiazepine, sleeping pills, and psychotropic medications, then you don't get rid of the problem.

I think you really need more data. You need to target the prescribing patterns of physicians, look at them, and if they are falling out of what we consider norm there needs to be some intervention.

But education is not going to simply correct the problem.

The CHAIRMAN. Well then, doctor, you believe the key is the prescribing physician?

Dr. COLINGER. Yes. I believe the key is the prescribing physician.

The CHAIRMAN. Doctor Avorn.

Dr. AVORN. I agree.

The CHAIRMAN. Doctor Simonson.

Dr. SIMONSON. Yes.

The CHAIRMAN. I agree. I think that is absolutely the key. And I would agree with you, Doctor Avorn. The physician is key. I think that is true, because pharmacists are going to, by and large, fill the prescription that was given to them and rely on the physician's judgment.

Dr. SIMONSON. Actually, Senator, if I may interject: a pharmacist really does have responsibility to counter-check and double-check what the physician has prescribed. Certainly in the nursing home, now, the pharmacist is required to review—as I am sure you are aware—drug therapy on a monthly basis.

Many times there are multiple prescribers or allergies that the prescriber is not aware of. The pharmacist is sort of the overseer and coordinator of the drug therapy, but the physician is the prescriber.

The CHAIRMAN. Well, I recognize that as a responsibility of the pharmacist, but it is pretty difficult when a pharmacist gets a prescription and doesn't know how many other prescriptions have been given. In the nursing home that can be done.

Dr. SIMONSON. Right.

The CHAIRMAN. But in just general, the pharmacist is not in a position to know anything about the patient, and is not in a position to know whether that patient is taking a whole bunch of drugs. That might not be necessary.

I get the thrust of all three of your positions on this. It has to be coordinated. There are several key elements. I now ask Doctor Simonson: Do you agree that with Medicare and Medicaid patients there ought to be a screening process on how many drugs are being used by a particular patient through the computer system finding out and pinpointing when some patient is taking seven or eight different types of drugs at one time?

Dr. SIMONSON. This already is being done in certain Medicaid programs where the patient consumption is screened. Absolutely. You can find some very interesting——

The CHAIRMAN. What programs are those?

Dr. SIMONSON. Some studies have been done. I don't think it is a requirement on a national basis, but you can certainly learn a lot by having the computerized files.

Even if the patient is going to different doctors and different pharmacies you have centralized the information and can find out——

The CHAIRMAN. Because it is all there if you want to look for it.

Dr. SIMONSON. Absolutely. Yes.

The CHAIRMAN. All right. Now for the Food and Drug Administration. What more should they be doing? Doctor Avorn?

Dr. AVORN. I continue to await with interest the guidelines that we've been hearing about since the early 1980's. It is not clear to me what happened to them. FDA seems to have the sense that there is now enough movement in that direction spontaneously that we don't need to have guidelines; but I don't share that view. It is difficult to expect that industry will voluntarily slow down the drug approval process, which it might have to do to include complicated, elderly people in the testing, when that could be a very major financial negative for them.

It is perhaps being naive to expect that they are going to be doing that on a large scale voluntarily. We might need to codify some requirement that older people be included in the pre-marketing testing in a systematic, nontrivial way before a drug is allowed to be on the market if it is going to be used primarily by the elderly. We have not gotten very far with voluntary compliance, I don't think.

The CHAIRMAN. First of all, let me assure you we will indeed find out what happened to those guidelines. We are not through with the Food and Drug Administration on that particular point.

Second, I think you are aware that they are not required by law to publish any guidelines. Would you recommend that Food and Drug Administration be required by law to publish guidelines?

Dr. AVORN. If this committee were to indicate that there were perhaps a 1- to 2-year time frame during which the Food and Drug Administration is expected to generate some useful and workable solution to this, failing that some legislation could then occur.

That strikes me as giving them enough notice that this is really something about which people mean business, but not necessarily bringing the legislative apparatus into play unless it turns out that nothing else is going to work.

The CHAIRMAN. Well, I think my colleague here—the former chairman—strongly recommended that several years ago. Am I correct, Senator Heinz?

Senator HEINZ. Mr. Chairman, you are correct, but nothing has happened.

The CHAIRMAN. Yes.

Senator HEINZ. My fear is that unless we, in fact, have a foreseen mechanism that is a good deal stronger than saying, "We'll enact legislation in 2 years unless you act," we will be right back where we are today, only 2 years removed.

I wish it wasn't necessary, Mr. Chairman, to tell an agency whose mission is to protect the public health and safety where medical practices are concerned, that they should be doing their mission. That is, essentially, what we are saying.

They are then forcing us to micro-manage as to how they do their mission. But since they aren't doing it, they don't leave us much choice.

Dr. AVORN. If I may respond to that, Senator Heinz: My impression from conversations with various parties is that both FDA and industry perceive the agency to be understaffed and underequipped to get drugs quickly onto the market. Some of the resistance on the part of industry to having the elderly mandated in the drug approval process is their fear that what is already a long process will become even longer.

Perhaps if something could be done simultaneously that such requirements are put in place to enable the FDA to move more efficiently than it currently does—perhaps by means of giving them the sort of staff support that they need—we might be able to speed things up at the same time that we impose the new requirement, and that might meet everybody's needs best.

The CHAIRMAN. Well, it would be great to have the Food and Drug Administration tell us exactly what they need, and I assure you they will be given that opportunity again.

As you might have noted at the outset of this meeting, we had invited Food and Drug Administration to this particular hearing. They said it wasn't convenient, and I accepted that because I realize that in many of the points that are raised here they are not going to be able to respond.

Dr. AVORN. It is important for us to distinguish what the FDA can and should be expected to do, versus things which we need to expect from somewhere else in government or in other parts of society.

The FDA really, should be expected to do a good job of approving drugs for use and establishing guidelines; the labeling discussion earlier today was important in this regard. However, the FDA can't be expected to somehow regulate the quality of prescribing if the drug is a good drug and is on the market. That is something which it doesn't have the apparatus or the mandate to do.

It needs to get drugs approved and labeled well, and after that we really need to look to other avenues if we are worried about the quality of prescribing of otherwise acceptable drugs.

The CHAIRMAN. Yes, I think we do recognize that this is only part of it, and there are some other key parts which we have already spoken to.

I don't know that we have covered everything that needs to be done or needs to be implemented at this time.

Senator HEINZ. Mr. Chairman, I hope not. If you have there will be no questions for me to ask.

The CHAIRMAN. No. I am sure we haven't.

I would like to make a part of the record at this point, since we have been discussing this, the response of the Department of Health and Human Services for Food and Drug Administration. We will do so. Quite a bit of data is involved there. They have expressed their willingness to be with us at a later date.

[The information to be supplied follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

March 23, 1988

The Honorable John Melcher
Chairman, Special Committee on Aging
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

I write to respond to your letter of March 15, inviting me to testify on March 25, 1988 before the Committee on FDA's activities related to the safety and effectiveness of drugs prescribed for older Americans. I appreciate your understanding of why we are unable to accept as we discussed with your staff. The significant and complex nature of this issue requires that we allow adequate time to prepare so that we might provide you with information that is both meaningful and complete.

I assure you that the Agency continues to play an active role in improving the use of drugs in older Americans. Enclosed is a brief description of our activities.

If you would like any additional information to be submitted for the hearing record, please let me know.

Sincerely yours,

Frank E Young
Frank E. Young, M.D., Ph.D.
Commissioner of Food and Drugs

FDA's Activities Related to Drugs Prescribed for Older Americans

We have been increasing our knowledge of the effects of drugs in this age group by encouraging the participation of older subjects in the testing of drugs and will soon finalize guidelines for premarket testing of drugs in the elderly. Although these guidelines are still in draft form, they have had a major impact in providing discussion of innovative ways to determine all of the factors, such as age, that can influence drug pharmacokinetics. The guidelines are already being implemented in that the pharmaceutical industry is utilizing them. In addition, we have published a proposed Guideline for the Format and Content of the Clinical Data Section of a New Drug Application which emphasizes the need to analyze data to search for any relationship of both favorable and unfavorable responses to age, and to conditions common in older patients, including abnormal kidney function, multiple diseases and drug therapy. Furthermore, FDA provides Institutional Review Board (IRB) education through workshops and the dissemination of information sheets to ensure that premarket testing adequately considers the needs of older people. An IRB governs the review and conduct of all human research at a particular institution involving products regulated by FDA.

In addition, we now have more knowledge regarding the effects of drugs in older Americans through post-marketing surveillance monitoring which is primarily based on adverse drug reaction reports generally submitted by the practicing physician. The purpose of surveillance monitoring is to provide new information of drug risks that can be used for modifications in drug usage.

FDA has also been involved in interagency cooperative efforts relating to the health needs of older Americans, including the area of medications. One example of this is the "Surgeon General's Workshop - Health Promotion and the Aging," which is taking place this week. Under the direction of the Surgeon General, FDA has taken a major lead in the staffing, planning and execution of this workshop. The workshop will use invited experts to consider aging issues and develop a set of recommendations that will serve as the core for the Public Health Service efforts. FDA is coordinating the worksession entitled "Medications and Geriatrics." Attached is a copy of the work paper that is being used at this session.

Another FDA activity for improving the use of drugs by older Americans is in patient education. FDA has had a long tradition of working with major national and community-based organizations to develop programs and materials to advance public health goals to improve the health status of older citizens. During the last six years the Agency has been coordinating the development and implementation of significant patient education programs with the National Council on Patient Information and Education (NCPIE) which is a nongovernmental group of some 240 health organizations. FDA and NCPIE sponsored the "Get the Answers" compaign which is a program urging patients to ask their health professionals questions about their prescriptions. The major component of the campaign is a medical data wallet card that lists the five questions patients should ask when they get a prescription. The "Get the Answers" message has been widely disseminated to consumers through news releases, advice columns, and other media. NCPIE commissioned a report, released in October 1987, "Priorities and Approaches for Improving Prescription Medicine Use by Older Consumers" and this past year sponsored a campaign to improve the use of prescription medicine by older consumers.

Other educational initiatives undertaken by the Agency, in conjunction with national organizations, include national conferences addressing areas of importance to older women and educational programs in such areas as health fraud, tamper-resistant packaging efforts, and osteoporosis. Attached is a list of activities that have been undertaken by FDA and national organizations to respond to educational needs of the elderly.

In 1985, FDA's Center for Drug Evaluation and Research (then the Center for Drugs and Biologics), disseminated a newspaper column entitled "Safety Sense" to weekly suburban newspapers nationwide through North American Precis Syndicate, Inc. This column provided specific information for older Americans to ensure their safe and proper use of medications.

In addition, FDA publishes materials and conducts meetings across the Nation to address issues affecting the elderly population including drug use in older Americans. Specifically of interest are two articles reprinted from the FDA Consumer magazine, "Medicine and the Elderly" (September 1983), and "Questions About Your Medicine? Go Ahead--Ask" (October 1987). Our activities also include a major campaign to encourage health professionals to provide drug information to their patients.

Moreover, Parke-Davis gave a presentation to FDA on March 9, on the firm's Elder-Care program. This program, which is directed to the elderly, provides basic information on drugs, drug-taking, drug firm's Elder-Care program. This program, which is directed to the elderly, provides basic information on drugs, drug-taking, drug reactions, and drug contraindications. We are now considering the utility of incorporating some of the Parke-Davis materials into programs for the elderly. In fact FDA intends to make drug information for the elderly a major priority for the Agency in its Action Plan Phase III.

Attachments

Health Promotion and Aging
"MEDICATIONS AND GERIATRICS"

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I. Introduction and General Overview

Health promotion and disease prevention in the elderly is both appealing and worthy of our attention. While old age is not preventable, much of the disease and disability which is common in late life is preventable.[1] The rational use of medications, at both the policy and clinical level, has an important place in achieving this end, providing an important component in a health promotion strategy for healthy aging. Rowe and Kahn have cautioned against a "gerontology of the usual."[2] The focus on typical aging as "normal" ignores the enormous heterogeneity in this population. . This may mislead scientists and policy makers to view what is "usual" as a reasonable health objective for older Americans.

II. Basic Demographics and Population Data

In 1987, about 12% of the U.S. population is 65-years or older. By 1990, the 65 and older group will reach 12.7% of the population; by 2000 the percentage rises to 13.1; and by 2020, to 17.3%. By the year 2020, the 65 and over population will have increased by 102%, compared to the 31% growth for the entire U.S. population for the same 40 year period.[3]

Changes will also be taking place within the elderly population itself. Not only will there be more citizens over 65 years of age, both in absolute number and percentage, but individuals within this age group will be living longer and, on the average, may tend to be more frail, and possibly in greater need of medical care. The older age groups, especially those over 75, will increase most dramatically. The current number of persons over 85 (2.7 million) will double by the end of the century. Conservative estimates to the year 2050 indicate that at least 50% of Americans will survive to their 85th birthday, with the 85 years and older population constituting at least 15 million people.[4]

III. Health Characteristics

Three general health characteristics of older U.S. residents are relevant to medications and geriatrics. First, the pattern of health service utilization influences the opportunities for receiving a prescription; second, the epidemiology of disease (especially chronic disease) influences the duration of treatment; and third, drug activity in the aging body influences therapeutic safety and efficacy.

A. Utilization of Health Services. Prescription drugs are prescribed for the elderly primarily as outpatients making physician office visits, as inpatients in long-term care facilities, and as hospitalized patients, as well as upon discharge from health care institutions. Persons 65 and older account for 20.5% of physician office visits in 1985.[5] And while most elderly are not in nursing homes, they did occupy 88% of the available nursing home beds in 1985.[6] And in 1986 persons 65 and older accounted for more than 40% of the hospitalizations in this country, staying an average 8.5 days compared to 6.8 days for 45-64 years of age.[7] "In the near future, the majority of all users of health and health related services with the exception of obstetrics and pediatrics will be persons over 65."[8]

B. The Epidemiology of Disease. As briefly discussed above, the elderly in America are more likely to use health services than are younger age groups.[8] This is explained in part by the fact that in spite of fewer acute illnesses, their recovery time is often longer; the fact that they are nearly twice as likely to suffer from a chronic illness; and the possibility that they may overuse services relative to true need.[9,10] In view of this reality the health care system's response requires strategies that are often quite different than those for younger persons because of the following:

the prevalence of chronic disease. Eighty percent of persons 65 years and older have one or more chronic diseases. Certain of these diseases are largely age dependent, such as coronary artery disease and dementia of the Alzheimer's type; other diseases, such as most cancers, are considered age related.[11]

multiple pathology. The existence of several simultaneously active conditions is much more prevalent in the aged than in those younger.

nonspecific presentation of disease. Several diseases which occur at all ages have a different natural history in the elderly. Almost any of the classic signs or symptoms of disease are present in the elderly in uncharacteristic ways. Instead of usually anticipated presentations, diseases often give rise to nonspecific problems which may be incorrectly identified as due to aging rather than due to disease. These nonspecific problems include falling, dizziness, acute confusion, new incontinence, weight loss, failure to thrive, etc.

silent presentation of disease. Especially likely to be obscured in the elderly are pulmonary embolism, pneumonia, cancer, acute surgical abdomen, thyrotoxicosis, depression, drug intoxication, myxedema, myocardial infarction, alcoholism.[12,13]

C. Pharmacokinetics and Pharmacodynamics of Drugs. Drug disposition in the body of an elderly patient may be quite different than in a similar patient forty years younger. Although these changes may not necessarily occur, when present they are largely the result of age related changes in body composition, renal and hepatic function, and concurrent disease states. In addition, an older patient may not respond to a given drug concentration in the same manner as a younger individual.[14,15] Age related physiologic changes in older patients dictate that while the standard guidelines for applying pharmacokinetic principles often apply, they must be approached with caution because some of the usual assumptions may not be valid. In particular, the clinician must more carefully consider possible changes in body composition and vital organ function.

ABSORPTION / A number of aging-related physiologic changes occur in the gastrointestinal tract (GI) which increase the possibility of altered drug absorption. With advancing age intestinal blood flow may decrease; muscle tone and motor activity in the GI tract may decline; and mucosal cells may have atrophied, reducing both gastric secretory and absorptive function. The elderly demonstrate prolonged and widely variable gastric emptying times when compared to younger groups.[16] In addition, the pH of GI fluid is increased in the elderly, a change that may effect the absorption of calcium.[17] In spite of these demonstrated and theoretical GI changes, altered absorption does not appear to be a clinically important factor in dosage calculations for older patients.[18]

DISTRIBUTION / Body composition undergoes noteworthy changes over a lifetime of 70+ years. Body fat increases, muscle mass decreases, and total body water decreases. By age 70 greater than 30 percent of body weight in a given individual may be fat. On the other hand, muscle mass contributes a smaller proportion of body weight, declining by an estimated 25 to 30 percent by age 70. Total body water decreases in the elderly from 13 to 18 percent.[19,20] These changes can have a clinically significant impact on the distribution of both water soluble and lipid soluble drugs. As a rule, with substantially increased age, water soluble drugs will have decreased distribution, while lipid soluble medication will have increased distribution.

The plasma protein binding of drugs in the elderly may be altered.[21] The two major plasma proteins are albumin and alpha-1-acid glycoprotein. Older patients often have a lower than normal serum albumin level, usually the result of decreased albumin production. Also, an increased level of alpha-1-acid glycoprotein has been associated with advanced age.[21] The potential significance of these changes are either an increased free fraction of drugs bound to albumin (e.g. warfarin, phenytoin) or decreased free fraction of drugs bound to alpha-1-acid glycoprotein (e.g. lidocaine, propranolol). These alterations in binding may lead to the erroneous clinical judgments based on misinterpretation of serum blood levels.

METABOLISM / Phase I oxidative metabolism can be impaired in the elderly patient due to decreased microsomal enzyme activity. Also, the metabolism of drugs with high hepatic extraction ratios can be impaired due to a decrease in hepatic blood flow.[22] This is particularly important when prescribing certain drugs such as diazepam, quinidine, theophylline, propranolol, and imipramine. Easily estimating the extent of impaired metabolic function is not currently possible; consequently, dosage adjustments necessitated by metabolic impairment are, at best, estimates based on investigational and clinical experience.

Hepatic Phase II metabolism via conjugation is not meaningfully altered with advancing age. Consequently age related changes in clearance of drugs metabolized by glucuronidation clearance have not been reported. For example, oxazepam, lorazepam, and temazepam doses need not be reduced in older patients on the basis of hepatic function alone.

ELIMINATION / Glomerular filtration rate (GFR) declines steadily with increasing age. Because of the typical decline of muscle mass with advancing age, production of creatinine also declines. This produces serum creatinine levels usually considered normal for younger persons, but unreliable as an indicator of renal function in the older person. Thus, a calculated creatinine clearance is recommended when considering the proper dose of such drugs as digoxin, cimetidine, many antibiotics, and active metabolites such as N-acetylprocainamide and normeperidine.[23,24]

PHARMACODYNAMICS / The term pharmacodynamics usually refers to the magnitude of pharmacological effect that results from the interaction of drugs with receptors at the site of action. There is little information about the pharmacodynamics of drugs in the elderly, but an increased "sensitivity" to a number of drugs has been reported.[25,26] Perhaps the most widely reported is the enhanced pharmacological effect of narcotic analgesics in the elderly.[26,27] In a study by Kaiko it was found that elderly cancer patients, who received intramuscular morphine post-operatively, had significantly greater total pain relief and duration of pain relief than their younger counterparts. No information regarding adverse effects was reported.[28] This study confirmed similar findings reported in an earlier study by Bellville, et al.[29] Demonstrating decreased pharmacodynamic sensitivity, Vestal et al. have reported a reduction in response to both beta adrenergic agonist and antagonist drugs in the elderly.[30] From these and similar reports there is some evidence that age-related pharmacodynamic changes can occur. For the most part whether these alterations are due to diminished homeostatic mechanisms, chronic disease, or changes at the receptor or post-receptor remains to be determined.[25,26]

IV. Areas of Particular Interest

Medications are usually beneficial, sometimes of no value, and on rare occasion detrimental in their contribution to the health of the elderly. Numerous areas are of particular interest with regard to drugs for older patients. The few areas discussed in this background paper are the extent and pattern of drug use among older patients; the health promoting benefits the elderly derive from medications; their susceptibility to untoward effects of drugs; the potential for new technologies to benefit the elderly; successful interventions and programs; and selected deficiencies in current programs and services.

A. The Extent of Drug Use. The elderly take prescription and non-prescription drugs to a greater extent than younger persons. This appears to be so because their greater use of health services makes them more likely to receive prescriptions or make self-medication decisions.

PRESCRIPTION DRUG USE / As previously mentioned, the elderly make up 12% of the U.S. population. It is estimated however that this group accounts for approximately 30% of all drugs prescribed in the U.S.[8,31] In 1982 all consumers spent $14.5 billion for prescriptions dispensed by community pharmacies.[33] The elderly's precise proportion of that cost is not known, but if it was 30% that would be $4.35 billion. An FDA study found that those over 75 years of age received the most prescriptions in 1982, averaging almost 17 annually. The "young-old," those 65 to 74, received only 13.6 that year. These numbers are much larger than the averages of those in the 55 to 64 age group (9.3 prescriptions) and the 45 to 54 age group (6.9 prescriptions).[32]

The 1985 National Ambulatory Medical Care Survey of office based physicians found that elderly women accounted for 12.5 percent of all visits and 17.7 percent of visits in which drugs were prescribed; elderly men accounted for 8.0 percent of visits and nearly 11 percent of visits involving drug prescription.[33] Overall at least one drug was prescribed or provided in over 68 percent of office visits by those 65 years of age and older.

OTC DRUG USE / Self medication as part of self-care seems to be one of the most important and frequent health maintenance actions taken by the elderly. A recent study of rural elderly found 65% of those surveyed to have used over the counter (OTC) medications in the previous two weeks, with women taking more than men.[34] This was consistent with findings from an earlier study of an elderly population in which 64% had taken OTC medications; again, women used more than men.[35] Respondents in this study reported consuming in a one day period an average of 1.74 prescription drugs and 1.13 over-the-counter drugs.[34]

B. Patterns of Drug Use. Drug use patterns in the elderly vary according to the populations in which data is collected. The best defined data comes from ambulatory elderly populations. Two ongoing programs, the Dunedin Program in Florida and the N.I.A.'s Established Populations for Epidemiologic Studies of the Elderly (EPESE), provide the most extensive and detailed information about both prescribed and OTC medications in a controlled study population or cohort. The Dunedin Program which has screened approximately 3,000 elderly each year since 1978 for undetected medical disorders, has also collected patient-recorded information about prescribed and OTC medication. Over a five-year period 93% of patients in that population took some medication, with a mean of 3.7 medications at the time of interview. The study also found women to be consuming more than men, and drug use increasing with advancing age.[36] The most common therapeutic indications for all drugs were antihypertensives, non-narcotic analgesics, antirheumatics, various vitamins and cathartics. Striking changes over the five year period include an increase in mean drug use (from 3.2 medications) and a considerable increase in nutritional supplement use.[36]

The EPESE project, a community-based surveillance program funded by the National Institute of Aging, is being conducted at four research sites; New Haven (Yale University), East Boston (Harvard University), rural Iowa (University of Iowa), and the Piedmont area of North Carolina (Duke University). Extensive information regarding both prescription and OTC medication use is being collected as part of these in-home surveys of between 3,000 to 4,500 community elderly. The first published report of medication use in an EPESE population was from Iowa where 88% of patients took some medication, with the mean being 2.87 drugs. In this population medication use increased with age and was greater in women.[34] The most common therapeutic indications for drugs were cardiovascular, analgesics, vitamins and nutritional supplements, gastrointestinal products and CNS agents. Analgesics, vitamins, and GI agents (e.g., laxatives) were the most frequently taken over-the-counter therapeutic categories in Iowa among rural elderly.[34] In fact, products classified as "analgesics and antipyretics" constituted over 39% of the reported OTC drug use; and three most frequently mentioned categories accounted for more than 94.1% of this use. While the Dunedin and Iowa populations and methods are not comparable, the most distinguishing difference is the apparently greater use of drugs seen in the Florida population.

Additional information about commonly prescribed medications for ambulatory elderly comes from a variety of sources. The most recent information (1986) is from two electronic data bases: IMS America Ltd. (Ambler, PA), and Pharmaceutical Data Services [PDS] (Scottsdale, AZ).[37,38] The top five therapeutic classes prescribed for the elderly according to the IMS data were digitalis preparations, diuretics, beta-blockers, nitrates, and antiarthritics. The PDS data, reflecting prescription drugs dispensed, showed the top five drugs for the elderly to be hydrochlorothiazide and triamterene, digoxin, potassium chloride, nitroglycerin, and furosemide.

Drug use patterns from institutional settings are less well defined. A 1976 survey of long-term care facilities found that most patients received between 4 and 7 medications with the mean being 6.1 drugs.[39] The most common therapeutic indications were cathartics, analgesics, tranquilizers, sedative/hypnotics, and vitamins. According to PDS, the top five drug products dispensed to elderly nursing home residents in 1986 were digoxin, furosemide, potassium chloride, dipyridamole, and nitroglycerin.[38] This pattern reasonably reflected the frequency of use these products had among non-institutionalized elderly that year. In alarming contrast, the sixth and seventh ranking drugs among elderly nursing home residents were haloperidol and thioridazine HCl; among non-institutionalized elderly these same agents ranked 99th and 90th respectively.[38] This report also revealed that during the first quarter of 1986, 59.2% of the elderly in the nursing homes received 4 or more prescriptions, compared to 35% of the non-institutionalized elderly.

Drug usage in hospitalized elderly is available from a variety of sources. A drug use surveillance project on a geriatric specialty unit found 500 of 521 patients to be given medications. Patients observed during the study period were given an average of 6.1 medications. In order, the most frequently used drugs were diuretics, antibiotics, bronchodilators, and analgesics.[40] Another study of 56 hospitalized elderly patients reported the mean drug use to be 4.1 medications prescribed for chronic use with the most common therapeutic indications being cathartics, analgesics, vitamins, diuretics, and cardiac drugs.[41]

C. Health Promotion Benefits of Drug Therapy. Health promotion strategies, particularly in older populations, must clearly rely on both social-behavioral and medical strategies. Many maladies of old age can be traced to health risk behaviors of young adulthood, and as a result prevention is often viewed as having little value as a health strategy after 65 years of age. Kannel and Gordon have suggested "that because of the relatively high incidence of mortality in the elderly the absolute impact of preventive measures short-term may actually be greater in the elderly than the younger despite a lesser relative impact."[43]

Since that suggestion, made in 1977, the preventive value of treating diastolic-systolic hypertension in the elderly has been demonstrated. The V.A. cooperative study demonstrated a 54 percent reduction in fatal and nonfatal cardiovascular events in the 60 years and over age group.[43] The Hypertension Detection and Follow-up Program found that older patients receiving drug therapy according to structured guidelines (otherwise termed "stepped-care") had lower incidence of stroke and lower mortality than age matched controls referred to their usual "regular care" for management.[44] And, results from the European Working Party on High Blood Pressure in the Elderly Trial have shown dramatic reductions in morbidity and mortality among drug treatment subjects over a seven year period.[45] Of course the importance of attentive monitoring during treatment cannot be over emphasized; anti-hypertensive medications are among the most widely implicated contributors to adverse drug reactions in the elderly [reviewed later in this paper].

The efficacy of influenza vaccine was evaluated in nursing homes of Genesee County, Michigan, during the winter of 1982-83. Investigators found the use of influenza vaccine to reduce both incidence and severity of influenza virus infections among the elderly.[46] A positive cost-effectiveness analysis of influenza vaccination programs for the elderly was reported comparing medical costs and health effects between vaccinated and unvaccinated elderly from 1971-1972 through 1977-1978.[47] Despite belief in the preventive value of the vaccine, medical compliance with recommendations for its use has been poor; institutional policy appears to be the best means for accomplishing wide spread immunization.[48]

Disability and immobility are associated with fractures in older persons; and fractures are associated with low bone mass.[49] The N.I.H. estimates that about 1.3 million fractures a year can be attributed to osteoporosis in people aged 45 years and older.[50] As one of the most prevalent afflictions of advancing age, osteoporosis-related vertebral fractures burden one-third of women by age 65. By age 81 hip fractures, usually associated with osteoporosis, will have stricken one-third of the women.[51] An effective means of preventing the loss of bone mass in postmenopausal women is regular use of estrogen therapy, particularly when combined with calcium supplements.[52,53,54] The FDA recently acknowledged this preventive indication to be an effective use of estrogens when taken for 21 or every 28 days and combined with calcium supplements and exercise.

A variety of useful but less well documented preventive and protective actions of drugs have been reported. For example, a case-control study of 300 cataract patients and 609 controls found a protective effect from long-term use of aspirin-like analgesics.[55] Such findings clearly require methodologic scrutiny and additional investigation. But they also ought to encourage the continuing search for agents with potential for preventive/protective impact on common disabling conditions of advanced years.

D. Health Risks and Problems Associated With Medications. The major areas of concern with regard to health risks and problems associated with geriatric drug therapy can be organized as bio-medical, behavioral, economic, and health policy/health services. Conversely, these areas also represent important targets for drug oriented health promotion interventions. In general, issues reviewed independently in this background paper (e.g. adverse drug reactions, compliance, costs, access, and attitudes) are very much interdependent, and an integrated approach to solutions is recommended.

DRUG RELATED BIO-MEDICAL ISSUES / Aging is associated with a variety of physical changes and health problems. Adverse drug reactions also present in a wide variety of symptoms throughout the body. A major challenge for the clinician is to distinguish between symptoms of aging and those associated with drug therapy. Mental disturbances, fatigue, depression, and syncope are examples of complaints that are associated with commonly encountered conditions as well as frequently prescribed medications.[56]

1. THE EPIDEMIOLOGY OF ADRs. Just as drug use patterns vary with populations, incidence and prevalence data for adverse drug reactions (ADRs) is quite dependent on data collection methods and settings in which studies have been conducted. Multicenter collaborative drug surveillance programs, voluntary reporting to FDA, cohort surveillance, the control phase of intervention demonstrations, institutional or population specific prevalence surveys, and computerized record linkage of secondary data sets have provided the most enlightening perspective on ADRs in the elderly thus far.

The Boston Collaborative Drug Surveillance Program (BCDSP) formalized and standardized clinical data collection on medication use and effects in a consortium of hospitals. Routine screening procedures have been used by BCDSP to correlate patient factors and drug response. From this effort dozens of adverse effects associated with drug therapy have been identified; advanced age has been an important variable in several instances (e.g. heparin in older women[57] and high dose flurazepam in older patients[58]).

The FDA has been collecting reports of suspected and known adverse drug reactions (ADR's) since 1968. The data has limitations because of the spontaneous and voluntary nature of the reporting system. Nevertheless, the value of summary information from this data set to alert researchers and clinicians to drugs worthy of more careful attention should not be overlooked. Recently FDA data from the 15 year period 1968-82 was tabulated to identify medications which may cause the older patient untoward effects.[59] From this analysis the five generic drug classes with the highest reported adverse drug reactions were identified. These were, in order, antiparkinsonian drugs, antibiotics, antiarthritics, antiarrhythmics and diuretics. The most recent data from FDA spontaneous reporting indicates an overall rate of 8.5 ADR reports per 100,000 population; the rate among those 65 and older is nearly double that.[60]

Drug induced admissions to hospital were examined along with other iatrogenic causes of hospitalization at a 769-bed urban teaching hospital.[61] In that institution 4.2% of admissions during two summer months were attributed to medication; half of which were considered by the investigators to be potentially avoidable. Medications accounted for 77% of all iatrogenic admissions. The average age among all iatrogenic admissions was 55 years. Another report of 293 admissions to a family medicine inpatient service found 15.4% to be drug-related with almost one-half occurring in patients 60 years of age or older.[62]

The occurrence of ADRs during hospital stays provides another perspective. During March and April of 1981 records for all admissions to Denver's VA Medical Center were reviewed.[63] In this study the occurrence of hospital associated iatrogenic complications for veterans aged 65 and older was compared with younger patients. The younger group had no complications caused by drug reactions while 17.7 percent of the older group experienced an ADR. This rate is consistent with those reported in other studies.[64,65] The differences between hospitals are perhaps due to the use of different criteria for determining a drug reaction.

Growing awareness of aging has stimulated an increasing number of investigators to use large computerized data sets to focus on drugs for their possible etiologic part in common problems of old age. Two examples for illustrative purposes are included. (1) An association between psychotropic drug use and hip fractures has been identified using computerized Medicaid files; dementia as a confounding variable did not appear to influence the results.[66] (2) A slightly increased risk of hospitalization because of gastrointestinal bleeding has been noted among elderly users of nonsteroidal anti-inflammatory drugs compared to nonusers at the Group Health Cooperative of Puget Sound.[67]

3. FACTORS CONTRIBUTING TO ADRs. It's estimated that at least 60 percent of adverse drug reactions are an extension of normal pharmacologic action.[68,69] Because most adverse effects are pharmacologic and usually well-known minor reactions, many should be preventable with more careful prescribing, monitoring, and patient education.

Elderly patients are at a higher risk of developing drug reactions than the general population. Several factors are known to predispose older persons to this excess risk. The first, and perhaps strongest factor is multiple drug use. Perhaps the first approach to preventing adverse drug reactions is to limit the number of drugs. This would not only reduce the chances of side effects occurring, but also reduce the possibility of drug interactions.[69]

Polypharmacy ... The incidence of polypharmacy or multiple medication use in the elderly is substantial.[34,38] One of the major associated problems is adverse drug reactions.[70] Williamson and Chopin found an increasing prevalence of ADRs as the number of prescribed drugs increased, occurring in 10.8% of those taking one drug and 27.0% of those taking six.[71] Another study of ambulatory elderly with dementia also found an increased incidence at ADR's with an increased number of medications.[72]

A number of factors contribute to the problem of polypharmacy.[73] Patients who use multiple physicians and pharmacies run the risk of receiving drugs that are therapeutic duplicates and drugs that interact since the health care professionals they see may not be completely informed about other prescriptions. In addition, there is a greater risk of medication errors and/or noncompliance due to polypharmacy.[74]

Pharmacokinetic and Pharmacodynamic Changes ... As previously mentioned, there are a number of possibly age-related physiological changes that may effect the pharmacokinetics of drugs in the elderly. There is a possibility of adverse drug reactions occurring when total body clearance of drugs is reduced either due to decreased hepatic metabolism or renal excretion. This risk is increased because the higher resulting plasma concentration should correlate with higher concentrations at the receptor site with an accompanying chance of enhanced pharmacological effects. In addition, regardless of pharmacokinetic changes, the elderly may experience enhanced pharmacodynamic response to drugs.

Often, however, it is difficult to determine which mechanisms, if not both, simultaneously contribute to adverse drug reactions. For example, a study from the Boston Collaborative Group has shown that at high doses of flurazepam (= or > 30mg) 39% of patients 70 years of age or older, experienced adverse drug reactions.[58] This compared to an incidence of 2% in the same group taking 15mg/day of flurazepam. A later study of flurazepam kinetics found a prolongation of its half-life in elderly men.[75] However, there are several studies of similar benzodiazepines in which the elderly had greater central nervous system sensitivity than younger subjects despite having the same drug plasma concentrations.[76,77]

Drug Interactions ... Traditionally, the term drug interaction (DI) has been defined as the effect -- either favorable or unfavorable -- that the administration of one drug has on another drug. Only a few studies examining DI's in the elderly have been reported. In a study of 573 hospitalized elderly, 2.16% of prescriptions written during their hospitalization produced potential drug interactions.[78] The investigators classified 78.2% of those interactions as avoidable or probably avoidable. Drug interactions in a 1975 nursing home survey of 562 patients were found in 5.8% of medication orders.[79] Another study of 132 nursing homes and 11,173 patients found that 2.7% of patients had clinically significant drug interactions occurring.[80] The occurrence of drug interactions among 1,094 ambulatory elderly was found to be much greater than that in the institutional populations (15%).[81]

It is not clear what proportion of potential drug-drug interactions are actually of clinical significance. For example, in one study 80% of the patients only required close patient monitoring as opposed to dosage reduction or drug discontinuance.[80] Still, the elderly are at an apparently increased risk for drug interactions as a consequence of the prevalence of polypharmacy. Also, in individual elderly patients who have altered homeostatic mechanisms and limited functional reserves, drug interactions may cause significant morbidity.

There are two major types of drug-drug interactions: pharmacokinetic and pharmacodynamic. Pharmacokinetic drug interactions occur when one drug alters the absorption, distribution, metabolism, or elimination of another drug. Interactions with the greatest potential for adverse drug reactions are those involving a decrease in the total body clearance of drugs with a narrow therapeutic index. For example, cimetidine has been shown to decrease the clearance of antipyrine, a marker of oxidative liver metabolism.[82] Pharmacodynamic drug interactions occur when one drug either enhances or diminishes the pharmacological effect of the other drug. This usually involves an interaction at the site of action or the receptor level. Of particular importance in the elderly is the cumulative effect of drugs with different desired pharmacological effects but similar side effects. For example, alcohol is reported to significantly contribute to sedation experienced by patients taking drugs with central nervous system depression side effects such as antihypertensives of psychotropics.[83]

Drug interactions in an even broader context include their adverse interactions with disease processes, foods, or laboratory tests. Drug-disease interactions, although less common than drug-drug interactions, have a greater potential to produce clinically meaningful adverse effects.[78,81] Information about drug-food (drug-nutrient) interactions is increasing.[84] It is well known that some foods can alter the pharmacokinetics of drugs, but drugs can alter appetite and/or cause vitamin deficiencies as well.[84] An area of current research interest is the effect of nutritional deficiencies on hepatic function and drug metabolism.[85] Drug-lab interactions (drug induced alterations of laboratory values) require careful evaluation and interpretation. They may indicate drug-induced illness or statistically significant, but clinically insignificant changes in laboratory test values. With growing interest in self-care and the in-vitro home diagnostic market, it will be imperative that patients and health care professionals understand that drugs may interfere with test results.[86]

3. BIO-EQUIVALENCE AND GENERICS. Generic prescription products provide a potential cost savings for the elderly. However, this potential has not been fully realized. The older consumer has shown reluctance to request generics in spite of potential savings. Reasons include perceived safety, efficacy, and financial risks; preference for the known product; and uncertainty about quality.[87,88,89]

There is a considerable debate about the use of generic drugs.[90] Since the passage of the 1984 Drug Price Competition and Patient Term Restoration Act, there has been an increasing number of generic products approved by the FDA.[91] One potential benefit of generics is that they are usually less expensive than brand name drugs. This should translate to cost savings for elderly patients. A recent study, however, questioned the cost savings of generic drugs and found wide variations in the prices of generic and brand name drugs.[92] Some have used this data to conclude that "it is not unusual for a generic drug to cost more than a brand name drug."[93] It is important to point out that in this study the consumer usually paid less for generics. Also, the study was conducted during 1984 before the new law took full effect.

Concerns have also been raised about the efficacy of generic drugs in the elderly.[94,95] This may stem from the fact that prior to approval for marketing, the studies required to prove bioequivalence are single-dose bioavailability studies of only 20-30 young health male volunteers. In addition, statistical variations as great as a 30% difference in generic vs. brand name drugs are acceptable.[96] Although the question of how this information specifically relates to the elderly patient is not fully answered, it is important to note that since 1984 there has not been a documented report to the FDA of a serious problem with a generic product.[96]

BEHAVIORAL ISSUES / The elderly appear to be particularly vulnerable to their own attitudes toward taking medications and the attitudes of others providing care. Straus has reviewed the complexity of behavioral issues as a risk factor in geriatric drug use.[97] Issues of compliance and attitudes provide a useful background to the larger topic.

1. COMPLIANCE. Assuming that a certain prescribed or OTC medication is beneficial, medication compliance or adherence is imperative to achieve therapeutic success. Numerous studies have shown, however, that whenever self administration or discretionary action is involved, patients frequently fail to take their medication as prescribed.[98,99,100,101] Patient noncompliance to prescribed therapies can have serious consequences. First and foremost, noncompliance can neutralize any therapeutic benefits of medical care rendered. Second, medication errors and/or medication noncompliance can lead to adverse drug reactions. Third, it has been associated with higher rates of hospitalization, longer length of stay in the hospital, and increased ambulatory visits, resulting in additional and unnecessary diagnostic and treatment procedures that generate avoidable costs.[102,103,104]

There is considerable controversy whether the elderly are less compliant with medications than younger patients. Two studies among noninstitutionalized elderly conducted 24 years apart reported an approximately similar medication error rate (59% and 50%).[74,96] Also, when the elderly were compared to a younger population, compliance rates were again similar.[105,106] Indeed, noncompliance seems to be associated with an increasing number of drugs rather than an increasing number of years.[107] An added dimension compounding the problem at the clinical level is the fact that physicians tend to overestimate their patients' compliance with prescribed regimens.[108]

Patient factors implicated as contributors to noncompliance include behavioral, social, and personal considerations. There is difficulty attributing health related behaviors, such as compliance, to the aging process. Not only are there methodological constraints (prevalence data vs. life course incidence data), but health behavior is also related to the social circumstances and historical context of an individual's life.[109] Nonetheless, an individual's perception and response to illness clearly influence his/her drug-taking behavior.[110] Eraker et al. have proposed a model for patient behavior which combines components Becker's earlier Health Belief Model and patient preferences.[111] This thoughtful approach to the issues of compliance contends that the matter is one of shared responsibility between physician and patient. One premise of this model is that the physician's responsibility is inversely related to the degree of patient participation; thus, the less responsible the patient, the more so must be the physician.

Social isolation has been found to play a significant roll in noncompliance.[112] A large proportion of older Americans live alone, increasing their likelihood of having compliance problems. In addition, one-third of the approximately 20 million Americans classified as illiterate are 60 years of age and older[113] compounding the potential risk of misunderstandings or lack of knowledge about therapy.[114] Other patient factors include personal impairments such as difficulties with vision or memory or learning disabilities,[115,116] and physical limitations imposed by arthritis or other handicaps.[117] There is also evidence that some nonadherence in the elderly may be intentional[118] and perhaps represent intelligent noncompliance.[119] In addition, it appears that economic issues play a role in noncompliance among older persons. A 1986 AARP telephone survey of a population (sample size not available) 45 years and older found 13% of those deciding against having prescription filled doing so because of cost.[94]

2. **ATTITUDES.** Provider attitudes may place the elderly, especially the poor elderly, at an increased for substandard medical care.[120] In spite of more prescriptions per office visit for older patients,[8] office practice encounter time with older patients is apparently less than with younger patients.[121] Perhaps this results from a perpetuation of the agism myths which Surgeon General Koop sees as self-fulfilling prophecies.[122] Wetle has suggested that this may partially be attributed to misapplication of population-based data.[123] Applying average life expectancy data in making individual management decisions deprives the patient of credit for surviving to the moment of care; the more appropriate issue is the life expectancy beyond this encounter for the individual patient.

ECONOMIC ISSUES / More than 30% of the national health care budget is spent on care for older Americans.[8] Nevertheless, this does not come close to covering the full expense of health needs of the elderly. Beyond this, out-of-pocket payments and third-party payors account for additional health expenses.

1. **PERSONAL EXPENSES.** A high rate of use and the large out-of-pocket expenditure for drugs place economic concerns on a par with safety and efficacy as important medication issues to be faced by the elderly. There are more elderly, and more of them are using more expensive drugs. Prescription prices in the U.S. rose 56% from January 1981 to June 1985; this far out-paced the Consumer Price Index which grew 23% over the same period. National telephone surveys by AARP in 1985 and 1986 found 62% of the elderly to be taking prescription drugs on a regular basis, with just less than half (45%) receiving some assistance from insurance or other health coverage. Among those without assistance the number of older patients paying more than $40 each month increased from 24% to 34%.[95] The extent of poverty (12.4% in 1986) among older Americans has remained at or near current levels for several years.[124]

Currently, Medicare coverage for outpatient medications moving through legal hurdles and final implementation. Overall, the potential cost of drugs under Medicare depends on the number of participants, the number of units per participant, and the unit cost of medications prescribed. Each factor is rising. In 1967 less than 78% of Medicare beneficiaries were taking medications; by 1980 the proportion had grown to more than 80%. Over that same period the average number of prescriptions per beneficiary grew from 10.4 to 12.1 annually. Because prescription size (doses dispensed) has increased over that same period the growth curves cannot be compared, but the average prescription cost more than doubled going from $4.00 in 1967 to $8.05 in 1980; in 1984 the cost for Medicare beneficiaries was over $10.00 per prescription.[125]

Although there are some state pharmaceutical assistance programs,[126] Medicare does not pay for outpatient drugs at this time. They will, however, reimburse for drugs administered as part of an office visit, with the notable omission of influenza vaccination. Perhaps Medicare use of health maintenance organizations in the future may change this policy.[127] For elderly patients that fall below a certain income level, Medicaid coverage of medications is available. In 1986 an estimated 6.6 percent of the elderly were covered by Medicaid insurance.[128] A recent study analyzing different Medicaid cost-saving programs found that the elderly had less access to "essential" medications [as determined by an expert panel (e.g., insulin, thiazides, furosemide, digoxin)].[129] The use of generic drugs may be an approach for patients and third parties to reduce medication costs.

New factors in understanding the cost of prescriptions are encountered each year. An estimated 5% of physicians are now dispensing drugs they prescribe, with nearly one-third of office-based MD's expected to do so "within a few years."[130] It's probably too early to appreciate the full impact of physician dispensing on drug costs for the elderly, but analysis by the Pennsylvania Department of Aging in the fourth quarter of 1986 found that elderly patients paid nearly $2.00 more per prescription when doctors dispensed the medication. The report did not indicate whether wholesale cost or quantity dispensed had been controlled in the analysis.[131]

2. **PAYMENT AND REIMBURSEMENT.** A major activity now under legislative consideration and enactment is the reimbursement of outpatient drugs for Medicare beneficiaries. Regardless of the exact outcome of this activity by the current Congress, this area will be of major interest for health economists and government officials for years to come. Although the primary concern of Medicare beneficiaries is the substantial out-of-pocket costs associated with prescription drugs, the primary concern of government officials is the cost of such a provision.[132] Given the finite dollars that Congress envisions for this benefit and the demographics of this benefit as a dramatic growth area, further refinement and adjustment will almost certainly occur with the introduction of the benefit.

At the request of the Health Subcommittee of the Senate Finance Committee, the Office of Technology Assessment (OTA) has submitted an examination cost containment strategies and possible approaches appropriate to drug coverage under Medicare.[133] Some (but not all) of the specialized cost-containment mechanisms offered for further exploration by OTA include various forms of price setting, provider and patient incentive programs, beneficiary cost-sharing programs, Federal grants to state pharmaceutical assistance programs, and developing a federal restrictive formulary.

Options for defining drug coverage under Medicare are limited. Comprehensive coverage, acknowledged by OTA to be the most expensive, might include all prescription drugs or all drugs prescribed for documented chronic diseases. Over-the-counter medications could be a component of this program. A limited coverage approach, on the other hand, could finance only selected therapeutic categories or targeted sub-populations (e.g., poor elderly or nursing home residents). Some options for specifying drug groups for coverage included determination of "life-sustaining" drugs by medical consensus, identifying drugs likely to prevent hospitalization with its associated costs, and approval only for drugs (or drug products) for which the manufacturer can demonstrate specific evidence of efficacy and safety when used by elderly patients. A third option available under Medicare is "phased-in" implementation drug coverage. This approach could allow for administrative consideration of changes in clinical practice standards, and benefit from accumulated program experience.[126]

HEALTH POLICY AND HEALTH SERVICE ISSUES / The delivery of health services and the implementation of health policy are indicators of society's expectations for health promotion. The drug component of a larger strategy is reflected in these selected examples.

1. MEDICAID. Although only 6.6% of the elderly were covered by Medicaid insurance in 1986, these were by definition among the least able to afford out-of-pocket health expenses.[128] Efforts to reduce costs and focus benefits under Medicaid have been a dominating health policy issue at the state level for several years. An analysis of the effects of a $1.00 copayment compared to a monthly limitation of 3 prescriptions found Medicaid's monthly savings under the two systems to be comparable.[129] However, the proportion of "essential" medications [see pg. E-10] obtained by recipients was greater under the copayment arrangement.

One approach has been the adoption of a generic formulary for Medicaid recipients by Alabama. Under that State's provisions, reimbursement for brand name drugs will not be made when generic equivalents are available. In another tack coverage of most anti-anxiety drugs was discontinued by Kansas; while coverage of psychotherapeutic drugs has been added by Arizona.[130]

Recently three states (Florida, Iowa, and North Carolina) adopted Medicaid service programs that are preventive in nature, but none of the three were directed at drugs or targeted the elderly. In 1985 Michigan adopted a therapeutic drug utilization program to identify Medicaid recipients at risk for drug induced illness.[131] In view of the higher rate of ADRs among the elderly, successes in this program ought to have greatest benefit for older recipients of Medicaid.

In view of the the increased general use of medications[58,59,132] (and psychotropic drugs in particular[58]), preadmission screening of applicants for nursing homes may shield some from overmedication while perhaps leading to more appropriate therapy for those admitted. Minnesota recently adopted a nursing home applicant screening program, and Massachusetts was considering the same in mid-1985.[133]

2. MEDICARE. An average 17% annual increase in Medicare expenditures between 1967 and 1983 prompted the shift to a prospective payment system based on diagnostic related groups (DRG's). This change in the reimbursement system was accompanied by increased rates of hospitalization for elderly Medicaid nursing home residents in Wisconsin.[134] Higher drug usage is usually associated with hospitalization; whether this occurred in this population is not known.

In spite of changes since 1983 Medicare costs continue to rise; and rising health care costs have financial impact on the elderly. In dealing with the issue the 100th Congress seems to favor an approach which will limit out-of-pocket health expenses to $2000 annually.[135] Proposals to expand Part B to include outpatient prescription coverage received wider support in 1987 than in previous years. Under consideration is a requirement that participating pharmacies would consent to offer medication counseling to all eligible program participants.

Prescription drug assistance under Medicare could include policy features designed to improve overall drug therapy. The OTA background paper on options for drug coverage by the Medicare Program included several policy features that might accomplish this end.[126] Among the options outlined were concepts of periodic professional review of drug regimens, limiting the number of prescriptions that can be funded, requiring a single dispensing pharmacy site, rewarding safety and toxicity studies targeted at elderly patients, and providing incentives for user-friendly packaging and labeling as well as patient education services.

3. HEALTH MAINTENANCE ORGANIZATIONS. Medicare recipients have been able to join an HMO since April 1985. During the two years following enactment of the legislation allowing this choice, slightly more than 900,000 (5.5%) of the eligible Medicare recipients had done so.[137] However, serious questions have been raised about the long term feasibility of a prepaid capitation system of providing health services for the elderly.[136,137] In some instances the actuarial basis for capitation payments does not reflect the population served; also, if treatments are influenced by financial self-interests the patient may suffer. In addition, a few early providers have allegedly devised enrollment campaigns which made access to enrollment sites difficult for frail or handicaped elderly. It is clearly in the interest of HMOs to promote health and prevent disease among their members; whether medications become an important facet of their strategy remains to be seen. There is some evidence that annual prescriptions per person is approximately unchanged in older subscribers but declines among younger subscribers following enrollment in prepaid health plans.[138]

4. PHARMACY SERVICES. Interest in mail-order prescription services has increased in recent years. Although its advantages and disadvantages have been debated in hearings and editorials, rigorous evaluation of the risks and benefits is lacking. Costs, counseling, error rates, convenience and access are the usual issues addressed. Proponents cite advantages that include savings due to an economy of scale, better ability to monitor therapy because of less "switching" between pharmacies, and convenience for less mobile patients.[139] Detractors claim higher error rates, less personal counseling,[140] and even higher costs. In 1985 an Arizona based study reported that a 4% savings in unit costs was offset by a 9% higher utilization by mail-order users.[141] It reported that changes in therapy for older users brought about more frequent ordering and increased wastage.

Labeling and packaging of prescriptions for older patients ought to take into account the possibility of visual impairments and confusion about products of similar size and color.[142] Many pharmacists use special services and "senior discounts" to attract the older patients. If such programs succeed in establishing client loyalty, the opportunity for regular counseling and ADR monitoring should benefit the older patient.

"Brown Bag" projects are programs in which elderly are encouraged to bring medications to a convenient location for review and counseling. Their focus is the ambulatory older population, and their purpose is to detect potential medication problems and correct those that need attention. One program has reported approximately 88% of participants need reinforcement, clarification, education, or health provider follow-up.[143]

5. FRAUD. The elderly seem to be less suspicious of medications that do not produce their promoted or expected results.[144] Among 172 older respondents (age 60 or older) to a 1984 survey, one-half reported purchasing a health product that did not work and just over one-half of those (53%) suspected it to be quack medicine. While appropriate cautions regarding interpretation were stated, the authors pointed out that the elderly are particularly vulnerable to fraud and the consequences of quackery because they are more likely to suffer from conditions for which many quack medications are promoted.

6. ADVERTISING. The claims that OTC as well as prescription drugs portray, either directly or indirectly, to the elderly are an area of continuing concern. Surveillance of the prescription drug claims relating to the elderly that are made directly to consumers or through health practitioners, will continue to share an area of high interest and surveillance by FDA.

E. Developing Technologies. New technologies in information management, drug products, and health service delivery bode well for improvements in drug therapy for the elderly. As computerized expert diagnostic systems become more user-friendly, the power of knowledge previously available only through years of experience should make extensive information available to all that care for elderly patients.[145] Public awareness of the special needs of older citizens has served to stimulate the application of new technologies in areas which benefit the elderly.

In the future, advances in technology are expected to result in the development of new dosage forms and new drug entities that will be more convenient for older patients as well as more specific and efficacious in their pharmacologic effects.[146,147] A number of novel drug delivery systems are currently being developed.[146] For example, transdermal delivery systems can extend a drug's duration of effect, and therefore should assist in improving compliance. Biotechnology advances are also expected to result in the development of numerous new therapeutic entities.[147,148] A number of pharmaceutical firms are currently working to develop new drugs that might reverse congnitive losses in Alzheimer patients.[149]

Geriatric assessment units have been referred to as examples of "new technologies" in health services, and have grown in number and scope since 1979.[150] A 1985 survey of 104 units found that nearly half had begun operation during the previous two years, and two-thirds of the others increased their capacity during that time. Most (approx. 60%) are outpatient units, and 27% of those reported "improvement in drug regimens" to be either their 1st or 2nd most important effect.

F. Successful Interventions and Programs. Drug related problems in the elderly do not usually occur in isolation. The several successful interventions reviewed here gave emphasis to a particular outcome (e.g., compliance, polypharmacy, adverse drug reactions, cost savings), but in most instances the intervention required multidisciplinary effort and cooperation, and effected more than one area of need.

COMPLIANCE / The success of drug-related health promotion patient interventions depends on relevance, individualization, feedback, reinforcement, and facilitation.[151] Ten strategies for reducing drug errors in the elderly were reviewed by Green et al. in 1986.[152] These investigators found facilitation to be the most common technique, with no more than half incorporating relevancy or individualizing intervention, and even fewer using feedback or reinforcement. They concluded that interventions combining interpersonal communication methods, visual materials and memory-aids had been shown to be effective means of reducing drug errors as well as related clinical symptoms in the elderly. Several of these studies compared the effectiveness of different strategies on medication compliance and errors. MacDonald, et al., found no significant difference between medication counseling and counseling with a medication calendar. Both strategies significantly improved compliance in comparison to controls.[153] Color-coded weekly medication packaging significantly reduced medication errors when compared to color-coded conventionally dispensed medications, medication counseling, and no intervention.[154] Another study compared verbal medication counseling alone and in combination with either written information, a medication calendar, or a seven day medication package.[155] Attitudes, knowledge, and compliance in an elderly ambulatory population were assessed. Drug knowledge was most favorable effected by verbal instruction alone or combined with a medication calendar. In contrast, patient reported compliance was improved only by the combined intervention of verbal medication counseling and use of a seven day medication package. In general, patients felt the interventions were useful with the notable exception of the medication calendar.[155]

EDUCATION FOR PRESCRIBING / There is some evidence that physician peer education can have positive impact on prescribing in general. Studies by Ray and Schaffner have shown that the prescribing of antibiotics and diazepam improves after receiving education visits from a physician.[156,157,158] Also, pharmacist provided drug information can favorably impact on the prescribing of specific drugs or therapeutic classes of drugs.[159,160,161] Avorn found improvement in the prescribing of cerebral and peripheral vasodilators, oral cephalosporins and propoxyphene after education visits by a clinical pharmacist. The program, involving 400 physicians, resulted in a 14% reduction in utilization.[159] Hanlon, et al., found the prescribing of the above mentioned medications and the number of medications prescribed per patient to be lower than national prescribing data in a family medicine residency program with an active clinical pharmacy program.[160] Finally, a controlled study showed that global prescribing practices were favorably impacted by continuing education provided by clinical pharmacists and pharmacologists.[161]

ADR REDUCTION and SAVINGS / Interventions by clinical pharmacists as consultants in long-term care facilities (LTCF's) have been documented as being effective. One study of feedback from the LTCF clinical pharmacist consultant reduced the incidence of medication errors, the number of inappropriate or unnecessary drugs, and the incidence of adverse drug reactions, thereby reducing medication and hospitalization costs.[162] In a long-term study evaluating the initiation, termination, and reinstitution of a consultant clinical pharmacist, it was found that there was lower drug-use, admission, discharge, and death rates during the time the consultant was with the facility.[163] A recent paper examining the cost-benefit ratio of pharmacist-conducted drug-regimen review in LTCF's estimated a net savings of $220 million nationwide.[163]

Another study monitored adverse reactions in 2,771 randomly chosen hospitalized patients during 1969-1976. Medications as well as indications for starting and stopping therapy were tabulated, and records for the 1969-72 period were compared with those for the 1973-76 period. An active surveillance and ADR reporting program during the second period resulted in a 61% reduction in the number of patients affected by reactions to drug therapy; with the greatest reductions in the two age bands over 70 years of age (69% and 89%).[164]

A novel study evaluating the pharmacist as a prescriber of drugs to previously diagnosed LTCF patients, found them to be more effective than physicians in terms of number of drugs prescribed, lower number of deaths, and increased number of patients discharged to lower levels of care.[165] The significance of this study may not be the role of the pharmacist as an independent mid-level practitioner but extrapolating this information to include the pharmacist as an integral part of a multidisciplinary team.

MULTIDISCIPLINARY COOPERATION / Nursing initiative at one teaching nursing home has targeted reduction in cathartic drug use as a priority.[166] In nursing homes conflicting schedules limit opportunities for personal contact and direct dialogue among professionals. Although drug regimen reviews conducted by nursing personnel in Iowa intermediate care facilities have identified a variety of problems, widely variable physician responsiveness to reports and recommendations has been reported.[167] In Georgia Longe et al. found that written recommendations of consultant pharmacists in skilled nursing facilities were usually effective, with 72% of drug-dosage recommendations and 80% of laboratory test recommendations being accepted.[168] In North Carolina an interdisciplinary team review approach to drug therapy recommendations resulted in a reduction in the number of medications at one long-term care facility.[169]

V. Priorities and Recommended Programs to Address Areas of Concern

THE AGING PROCESS and DRUG DEVELOPMENT / Basic research into the aging process and the diseases of aging is needed. Distinction between aging processes and disease processes is not possible in many instances.[170] Investigation into the physiology of aging will contribute to needed understanding of pharmacodynamic changes and guide drug development specifically beneficial to older patients. Health promotion and disease prevention initiatives should benefit from this basic research and, perhaps lead to the development of products that will enhance the quality of life in later years.

DRUG TESTING / In the past, there have been few carefully carried out geriatric clinical drug trials that investigated the pharmacokinetics and pharmacodynamics of drugs in older patient samples.[171] However, in recent years there has been a steady increase in information about these areas of interest.[172] FDA labeling guidelines were revised in 1979. These guidelines directed that prescription drug labeling feature special age group indications or precautions.[173] It is now common for FDA new drug applications to include analyses relating age with drug responses.[174] Evidently Phase III clinical trials are now less likely to have excluded subjects on the basis of advanced age. At FDA, Dr. Temple expects to have a formal drug testing proposal in place in 1987.[174] Although there are some disagreements about the specifics of the proposal,[175] a number of professional groups are encouraged by the FDA's requiring the inclusion of formal testing of new drugs in the elderly and improved labeling of such information. Once a drug testing regulation is approved, the clear need will be for more studies of currently marketed drugs (Phase IV) in older patients.

Clinical drug trials in which subjects are stratified on age and factors known to alter drug disposition are controlled. These studies are needed in order to identify agents for which pharmacokinetic changes are truly age-dependent. This approach to testing would provide elderly patients with maximum benefit at minimum risk and allow companies developing new drugs to inform prescribers of true factors effecting dose.

POST-MARKETING DRUG SURVEILLANCE / The field of pharmacoepidemiology, or the study of drug use and drug effects using specific epidemiological methods has emerged in recent years.[176] Interest in post-marketing surveillance (PMS) of drugs and their effects is evident in several sectors, including the government, the pharmaceutical industry, and third party payors.[177] Investigations carried out once a new product has been marketed (Phase IV studies) can include careful assessment of spontaneous reports, additional clinical trials, cohort monitoring, and case control studies.[178] Two primary objectives of PMS are an assessment of efficacy and toxicity under conditions of actual clinical use, and an evaluation of the relative impact on approved indications.[179]

There are a number of data-bases which investigators utilize to study drug use, some of which were previously mentioned in this paper. Recently, there has been great interest regarding the effects of non-steroidal antiinflammatory drug since they are so widely used in the elderly; several studies utilizing the Medicaid Drug Event (Compass) Data Project,[180] The Boston Collaborative Drug Surveillance Program,[181] The American Rheumatism Association Medical Information System (Aramis),[182] and the FDA data-base have been published.[183]

In view of the evidence that older patients are at higher risk of adverse drug reactions and may exhibit atypical response to therapy, PMS in populations 65 years of age and older seems particularly advisable. Presently there are limitations due to the inherent nature of the data-bases themselves,[184] and the lack of a comprehensive national system.[185] There are, however, encouraging signs that the field of pharmacoepidemiology will continue to emerge and play an important role in knowledge of drugs and the elderly.[186,187]

LACK OF TRAINED PROFESSIONALS / Specialized knowledge of clinically important pharmacokinetic and pharmacodynamic changes that often accompany the aging process are needed for prescribing for the elderly.[188,189] It has been persuasively argued that many problems associated with prescribing can be avoided,[69,70] and yet about half the physicians delivering care in geriatric assessment units have no special training in care of the elderly.[190] Specialty training programs in gerontology and geriatrics offer one approach to imparting the specialized knowledge needed to avoid such problems. Unfortunately projections of population growth, particularly in the numbers of frail "old-old", strongly support the contention that requirements for geriatric specialists over the next decade will not be met.[190,191,192,193] At present there are 66 geriatric medicine programs and 27 geropsychiatry programs in the U.S.[193] A new fellowship program to train 4-6 physicians in geriatric clinical pharmacology will begin in 1988.[194] At a broader and more basic level, medical schools are providing only minimal training of geriatrics.[191]

Federal law mandates that a pharmacist review the drug regimens of all LTCF patients. This regulation has resulted in decreased exposure to unnecessary drugs and an associated decline in the cost of drugs in nursing homes. In addition adverse drug reactions and subsequent hospitalizations have also declined.[163] Although this role is established, there are only three accredited pharmacy residencies in geriatrics, and ten funded geriatric pharmacy fellowships in the U.S.[195,196] A 1985 survey of U.S. Schools of Pharmacy found that 40 schools planned to incorporate an AACP developed text on geriatrics in their coursework.[197] At least 10 schools indicated plans to offer geriatrics courses not previously available. The Geriatric Education Centers (GEC) Program has also stimulated expanded training in geriatric drug therapy.[198]

Whether responsibility for drug therapy management of elderly patients should be a shared or independent exercised, there is agreement that neither medicine[199] nor pharmacy[196,198,200] will provide an adequate number of specialized practitioners in the near future. Interdisciplinary training programs designed to enhance cooperative relationships between physicians, pharmacists and nurse-specialists should shorten the period during which the elderly can anticipate the shortage of geriatric drug specialists.

REIMBURSEMENT FOR SERVICES / Among issues usually associated with Medicare reimbursement, medication for the elderly is not typically considered. However, the opportunity (or risk) to receive medications begins with access to the prescriber and so reimbursement policy that effects access will probably effect drug utilization patterns as well. The American College of Physicians has recently published a position paper on alternative payment approaches for Medicare in which it suggests that inequities in the present reimbursement system "induce physicians to provide technologic and procedural services as opposed to cognitive and interpersonal services such as history taking, preventive health care, or patient education and counseling."[201]

FINANCING / An immediate assessment of the probable financial consequences of ambulatory drug coverage under Medicare is needed. The potential impact of such coverage on prescribing, pharmacy services, and self-care practices has not been studied.[138]

VI. Summary

Drug therapy represents an important approach to promoting health in the elderly. Rational and judicious use of medications can enhance the quality of life for older patients with chronic diseases. Wide variations in body compositon and organ system function exist among older persons. Consequently the clinical management of individual elderly patients demands caution and an appreciation of the possible variations in drug response. Respect for these nuances in drug response are essential to rational prescribing for the elderly.

It appears that drug usage in the elderly is considerable in terms of medications taken and associated expenses. There are also patterns of medication use which, while easily understood, suggest the need for greater prescribing forethought in subsets of the 65 and older population. For instance, increased prescribing for and general use of medication among older women; an increase in the number of medications with advancing age continues into the ninth decade of life; and more medications ordered in settings where higher levels of care is provided.

Changes in pharmacokinetics and pharmacodynamics can contribute to adverse drug reactions in the elderly. Polypharmacy (a major reason for drug interactions) and non-compliance (particularly excessive dosing) can also contribute to the incidence of ADRs. It is often difficult to predict the specific cause making advisable the use of lower initial doses with careful dose escalation titrated to therapeutic response.

As new drugs designed specifically for geriatric needs are developed, as additional training programs are funded, as new technology raises health costs in general, and as the number of elderly over 75 increases, the questions of "Who pays?" and "How much?" take on even more challenging dimensions. The issues to be faced in providing affordable, safe, and effective medications for older people in the U.S. are plentiful today, but will surely be even more numerous beyond the year 2000. 1988 is not too soon to begin to address them.

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FDA/National Organization Educational Initiatives

The Food and Drug Administration has had a long tradition of working with major national and community-based organizations to develop programs and materials to advance priority public health goals to improve the health status of older Americans. Many of the issues and educational initiatives undertaken by the Agency address the health and welfare of older citizens including tamper-resistant packaging efforts, the development of clinical guidelines for drug testing in the elderly, national conferences addressing areas of importance to older women, and key educational programs in such areas as health fraud, patient education, sodium reduction, and osteoporosis.

Specifically, the following are examples of the many activities that have been taken by FDA and national organizations to respond to the health information and education needs of the elderly:

FDA/American Association for Retired Persons cooperative projects have included joint slide shows on nutrition/sodium reduction and on health fraud; Dr. Young has met with the AARP Executive Board to discuss priorities mutually-shared; and meetings between Dr. Young, top FDA officials, and national organizations including AARP to discuss such issues as tamper-resistant packaging and priorities for the FDA Action Plan.

FDA/National Council of Senior Citizens have worked together to present "train the trainer" programs for the Council's regional/local representatives on patient education on prescription medications and health fraud. The Agency has also presented a workshop at the Council's annual national conference on health fraud and the elderly.

FDA/Auxiliary to the National Medical Association have just recently launched a demonstration project to "train the trainers" in several ANMA regional locations to bring the patient education on prescription drug messages to the Black elderly and their families.

FDA/PHS Coordinating Committee on Women's Health Issues cosponsored the 1986 National Conference on Women's Health which included a separate panel session on the "Contemporary and Emerging Health Concerns for Older Women." In addition, the conference also addressed major conditions of importance to the older woman including osteoporosis, patient education and communication, cancer, and nutrition. The proceedings from this conference were distributed to over 10,000 public health professionals and educators throughout the country.

FDA/Key Agencies in the Public Health Service/National Osteoporosis Foundation sponsored the 1987 FDA Special Topic Conference on Osteoporosis as the first in a series of national fora under the National Conference on Women's Health Program to address the health concerns of women. Proceedings of this conference will be published in PHS Reports and disseminated to over 10,000 public health professionals and educators. The Agency has worked with the National Osteoporosis Foundation to involve the FDA Consumer Affairs Officers located throughout the country in the 1988 National Osteoporosis Prevention Week initiative which is sponsored by Congresswoman Olympia Snow and which will focus prevention messages to the younger, middle-aged, and older woman.

The CHAIRMAN. Senator Heinz.

Senator HEINZ. Mr. Chairman, thank you.

I want to apologize to both you, Mr. Chairman, and to the witnesses, that I had to absent myself. I had been trying to get down to the Soviet Embassy for a week to deliver a letter to the Secretary General, Mr. Gorbachev, on behalf of Yuli Kosharovsky and his wife who have been on a hunger strike for, respectively, 2 and 3 weeks, and to deliver the names of five additional refuseniks who have first-degree relatives in Pennsylvania, and also to deliver the individual petitions, each one, from several thousand teachers of the Hebrew in Pennsylvania and nearby New Jersey, also, on behalf of Kosharovsky, who has been denied 17 years, and whose principal vocation and avocation, now, is teaching Hebrew. This, apparently, is a serious offense, because they keep making his life pretty miserable.

So the Soviet Embassy did accept these letters, but it took them a little while to do so, simply because the Minister Counsellor was tied up with the Ambassador "cleaning up," as he said, after the Foreign Minister's visit.

The first thing I would like to do, Mr. Chairman, is ask unanimous consent to put into the record drafts that we have of the FDA clinical guidelines that were developed in 1983, 1984, 1985, and 1987.[1] These four drafts of the FDA's clinical guidelines for the protocols we have been discussing are—according to the people who are more knowledgeable than I—excellent, generally speaking. They all have one thing in common: they have never been allowed to issue.

My question to the panel is: In reference to a remark that one of the reasons that these had not been allowed to issue was that there was underfunding and understaffing in the agency.

As I understand, most of these requirements would principally require the pharmaceutical manufacturers to do additional work. They would require them to have a sub-sample of the elderly, whose results would be studied and interpreted as a subset of the study on the drugs—presumably the drugs that they would be most subject to taking.

My question is: Are the drug companies the people who are resisting this more than the agency? From what I understand, the Surgeon General is anxious to have such guidelines issued. If he is anxious and the people in the FDA are anxious, it would seem that there would be either some kind of pressure inside the agency that would be difficult, or some kind of external pressure.

Professor Simonson, Doctor Avorn, Doctor Colinger, any comments on that?

Dr. SIMONSON. Yes, Senator Heinz. I would like to call your attention to a publication that was recently released by the Pharmaceutical Manufacturers' Association entitled, "New Research and New Concerns. Pharmaceuticals for the Elderly."

This report strongly reinforced the need and the desire for the industry to work on geriatric studies. I think Doctor Avorn's comment about the fact that the studies may take longer is, I'm sure, a concern of the industry.

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[1] See appendix 4, Items 10–13.

But in my opinion—and I am not officially affiliated with the industry, but I know people in the industry—my opinion is that they are very willing to do this research.

As one anecdotal example, a gentleman I spoke with in a large pharmaceutical manufacturer told me recently that 70 percent of his company's drugs are purchased by people age 55 and over. So the industry is well aware that if they develop good research and good information and are able to design drugs for the elderly, it will not only help the patient, but it will help the companies.

Senator **Heinz**. Doctor Avorn, Doctor Colinger, would you generally agree?

Dr. **Avorn**. I don't have any insight at all as to why this has taken so long.

Senator **Heinz**. Doctor Colinger.

Dr. **Colinger**. I have no comment.

Senator **Heinz**. All right. Let me ask this: In my opening statement I referred to several things that the Surgeon General's working group recommended, and Professor Simonson touched on at least two of them at the conclusion of his opening statement.

Let me just refresh on them. First, that new drugs should have labels, including directions for use by the elderly, or indicating if no data are available.

Second, existing drugs should have information regarding use by the elderly added to the label. That is existing drugs.

Third, the FDA should implement its guidelines for clinical testing of drugs and the elderly—that is what we have just been talking about—especially sub-groups at risk.

Fourth, that all medical professional schools should include courses on basic concepts of pharmacology, especially risk and efficacy of drugs and the aged.

Is there any disagreement among any of you on any of those four points? I take it not.

[Chorus of no's.]

Senator **Heinz**. I am not surprised. The question then, it seems to me, since these will take place if there is either movement at the FDA or if we cause the FDA to move. The next question that occurs to me is: How can we get physicians to do a better job within the existing informational context.

In that regard, let me address a question to Doctor Avorn. The study of Pennsylvania physicians that I earlier referred to found what you could call an inverse relationship between physicians' knowledge of basic concepts and geriatric pharmacology and the length of time since they were licensed to practice or graduated from medical school.

That same study showed that doctors who rely largely on drug company advertisements for their pharmacological information also performed poorly on a test of these basic concepts. Does that data support the need for continuing medical education requirements for physicians?

Dr. **Avorn**. It definitely does. We return to the point of whether requiring educational experiences or requiring competence is the best way to go. I've indicated that I think that competence is probably more important to demonstrate than the fact that you took a course.

There really is an informational vacuum that exists for people who trained more than a couple of years ago, or even those who are training now.

And yet, our experience is that physicians would rather do a good job than a bad job. There is a tendency these days to perceive physicians as people who want to maximize income and minimize risk and that we are guided only by concerns of economics and legal issues. Yet most of us went into health care because we wanted to take care of sick people and make them better.

Many of us fail to do that in prescribing for the elderly, not because we are venal or evil, but because nobody has really shown us how. A lot of what we have been talking about today is information that wasn't available in a widespread way many years ago.

Based on that sort of naive and old-fashioned assumption, I would be very interested in a national program to get information out there to physicians and see whether if you could teach people about drug use in the elderly in a systematic way, they might do a better job.

I am not implying that that is the only thing to do, but an supporting a three-pronged approach. First, we should require physicians to demonstrate ongoing competence. Second, we should create the tools with which they can get competence, by having universities—teach physicians on an outreach basis, the way the drug companies have done for decades—much as we did with agriculture in earlier years, the idea of an "extension service."

Third, we need some flagging system through the various computerized networks that are now used to disseminate drugs to people, to see which physicians and patients are really getting into trouble and slipping through these educational and competency nets that we have created. This would go an enormously long way to reducing the misuse of drugs in the elderly.

Senator **Heinz**. As you, I know, are well aware, the drug utilization review component and requirement in both the House, and even more so the Senate, on Medicare prescription drug benefit legislation, is something that, frankly, you can take a good deal of credit for because of your work on both sides of the Capitol and both sides of the aisle to help show us the way to act on what we believe is a nonthreatening, but nonetheless very useful opportunity to gather information that would not otherwise be available, even, in many cases, to a physician, about the drug utilization of an individual Medicare patient. And to apply, through modern technology, a series of screens or devices to identify inappropriate utilization and, as you point out, to provide counselling— the word I would use—a form of education and intervention that hopefully would be very positive, very nonthreatening, and would lead to the result that we all want, which is a better educated prescriber or physician prescribing these very important medications.

Is there, in either of the House or Senate bills, any mistakes we have made, or improvements we should make?

Dr. **Avorn**. Thanks for those kind comments.

I don't know this week what the various versions look like in the conference committee.

Senator HEINZ. Neither do we.

Dr. AVORN. OK.

Senator HEINZ. At this point the staff is undertaking the role of "clearing out the underbrush." Hopefully that means they will throw no babies out with bath water, and not clear out any fruit trees along with the thorns.

Dr. AVORN. There was a misperception in one of the earlier versions—I think it might have been the Senate version; I'm not sure—which implied that there was a wealth of diagnostic information in Medicare that one could somehow tap into to see whether the drugs that were being prescribed matched what the diseases the people had.

That information really is not there. We work with Medicare data a fair amount on our computers, and that information is simply not present in the way it would need to be, nor do I think it would become obtainable over the next number of years.

So whatever is going to be looked at in terms of utilization would need to rely primarily on drug use patterns and not on the mistaken belief that there is diagnosis information that you could relate them to. That is one point.

The other is: I think that the ultimate bill will——

Senator HEINZ. And when you say "drug use patterns," what you are primarily focusing on is interaction?

Dr. AVORN. No, actually drug choices and dosing, themselves. That is, there are real questions about any use of a medication at a given excessive dose in an older person. Once in a rare while it might be appropriate, but that in itself—even if they are on only one drug, if it is an excessive dose that can be a red flag by itself.

And then, also, there is the possibility of using medications as markers for diagnosis. That is, if somebody is on a medication implying that they have an ulcer, you could then look at whether or not they are taking medications that would be bad for ulcers.

It is inferential, but it is at least a start. Since we are not being coercive about the outcome, it is something which is plausible to try.

What I did not find in either version, last I saw them, was any clear-cut way to operationalize any of this. That is, there were statements that the Secretary shall make sure that utilization is appropriate. What we need is something that is truly operationalizable, either in terms of a commission that would have responsibility for figuring out the details, or something specific in the legislation such that you could then call the Secretary in and say, "What are you doing about it?" Right now it is not clear what the Secretary is supposed to be doing in the versions that I saw.

Senator HEINZ. There is a provision in the Senate Bill which reads that the Secretary must publish standards for appropriate prescription dispensing and utilization of each drug. The Secretary must use authoritative medical reference to set standards. That is absent from the House bill. You are saying that is helpful, but doesn't quite go far enough?

Dr. AVORN. Right. There is now a fair amount of research in this field of how physicians make prescribing decisions, and it universally indicates that having state of the art statements, either in libraries or on their desks or some place else, doesn't really do anything. It makes people feel good, but it doesn't change behavior.

Senator HEINZ. What should we include in the legislation to bring about implementation?

Dr. AVORN. A program such as the kind that was described by Senator Domenici and the kind of work that we have been doing at Harvard the kind of work that has happened out at Vanderbilt University in which there is outreach by a medical school or school of pharmacy to physicians in a given region, such that there is responsibility on a region-by-region basis for creating educational programs on drugs and the elderly for doctors, and perhaps, also, for patients. This would be a very, very important foundation to get the knowledge base out there.

Senator HEINZ. There are a number of ways, I suppose, we can get there from here. One set of ways is by structuring a variety of new conditions of participation in Medicare for all kinds of people—for doctors, for hospitals, for nursing homes, for hospital pharmacies, for pharmacies that receive reimbursement under the new program for Medicare. There is a long list of opportunities to take that one approach, which is, as I say, a conditions of participation approach.

There are other options. Let me ask any of you which of those options should we most seriously consider, and when?

Professor Simonson, do you want to take a crack at that one?

Dr. SIMONSON. One development that we have seen in pharmacy education—continuing education—is the advent of what we call "certificate programs," which is a post-baccalaureate, not a degree, but a rigorous, structured program that a pharmacist already in practice can study contents of pharmacology and the aging.

I am not really sure if that should be a required condition for participation or should be elective. I think a lot of pharmacists are electing to enroll in these courses because of their self-perceived knowledge or that they don't have enough information on geriatrics.

Senator HEINZ. Well, would it be a mistake, at this point, to mandate any new conditions of participation for Medicare, either for nursing homes—an example would be, I suppose, that there be a new person at a nursing home who is trained in geriatric pharmacology or has some established level of competence defined, in some way, as a condition for reimbursement under the Medicare program to that nursing home. Now, is that a good idea, or a bad idea?

Dr. COLINGER. I would answer "yes and no." In regard to physicians, you know, the statement I made earlier was, "You can legislate education requirements, but until you get it across to the primary care provider that he is out of the norm as far as his prescribing habits, then you are not going to make a dent."

I can be perfectly well educated and still prescribe out of what we consider norm.

I would go back to the statement I made earlier, again, that what we really need is to identify these folks some way through Medicare or Medicaid in order to target them for education.

Now, in the nursing home environment it is really easy to make participate or drug utilization review as a mandate for their participation in the program. I think that is entirely accurate.

But, you know, in the overall scheme of things——

Senator HEINZ. So you would focus on the institution and require some kind——

Dr. COLINGER. I would in the nursing home.

Senator HEINZ [continuing]. Of DUR in nursing homes?

Dr. COLINGER. I would in the hospital. I'd do a little bit of something different with physicians, and I sure wouldn't neglect the patient and their family in doing something with them, because there is still a problem, even if the physician is educated, in that there are a large number of folks in out-patient medicine that are not in an institution that are going from physician to physician, and maybe those physicians are going to follow the norm in their prescribing, but if you throw the fact that they are going to three physicians, then they are going to end up with multiple medications that are unnecessary.

There has got to be some way of involving patients or a responsible family member into the overall chain of things, too.

Senator HEINZ. Doctor Avorn, Professor Simonson, would you generally agree with what Doctor Colinger said?

Dr. AVORN. To quote Doctor Colinger, "Yes and no." I think there is a real risk. There are a lot of examples in long-term care of paper compliance. I mean that well-intentioned regulations are often promulgated out of Washington, because it seems like they would work. We then often find that people discover ways to comply on paper with the letter of the regulation, but the entire spirit of what it was about gets lost in the shuffle. This happens in nursing homes all of the time. So I am a little worried.

For example, there is in place—and has been for many, many years—a Federal requirement that there shall be a pharmacist reviewing the medication records of every nursing home patient. And there are people all around the country who do that all the time, every month. Some of them do it very well, and some of them do it very, very poorly.

It is possible for the person who does that review to be employed by the pharmacy that provides the medications for the nursing home, and there is a built-in—in my view—conflict of interest. If you are a company selling the drugs to a given nursing home, you are probably not the one who is going to come in on a white horse and say, "Let's reduce all the medications, as Dr. Colinger has done, by a significant factor," because you would be cutting your own throat economically. But there is paper compliance to that "review" process.

I do not share the view that education is unimportant in and of itself. It is important; if we had a better educated population of physicians out there they would probably be doing a far better job. We could then pick up the outliers, perhaps, by looking at profiles of excessive use.

Dr. COLINGER. I didn't mean to imply that education is not important.

Senator HEINZ. I just want to ask one last question, and then I want to yield to Senator Pressler. This is for you, Doctor Simonson:

You point out that physicians are often apparently unaware of the appropriate geriatric dose for a given drug, even if the manufacturer has included that information in the product labeling and ads. Have I understood your testimony correctly?

Dr. SIMONSON. That is correct.

Senator HEINZ. That has to be troublesome to the Congress, that they disregard available information. In this case, here is the information. Only if the doctor is dyslexic or needs new eyeglasses can you really understand why he doesn't avail himself of the opportunity to read about the drug.

Should we just wait on the kind of education effort that Doctor Colinger has indicated? Or should we do something more aggressive?

Dr. SIMONSON. I think probably the reason why that occurs is that there are a number of prescribers that don't have a full appreciation of the needs of the elderly patient. In that type of situation an interdisciplinary program, such as a pharmacist-nurse-physician working together, can arrive at the proper dosage.

Whether or not we should require increased educational programs for conditions for participation, at this point I am not really sure.

Senator HEINZ. All right.

I thank you all.

Since I know Senator Pressler has an appointment in a few minutes I will yield to him.

Senator Pressler.

STATEMENT OF SENATOR LARRY PRESSLER

Senator PRESSLER. Well, I shall yield back very quickly.

First, I should say that I do have a prepared statement that I would like to place in the record.

I am very interested to learn how adverse drug reactions affect the elderly in smaller cities and towns in rural America. However, I understand that there is very little difference between rural and urban areas. Our witnesses agree with me on that point.

I would like to show a blister pack developed by ASCO of Silver Spring, Maryland. The elderly can take their prescription drugs by pushing the blister containing the pills for that day.

Taking medication is much more of a problem for the elderly than many of us realize. It is easy for them to get their pills mixed up.

The elderly in South Dakota are currently using another similar type of user friendly devise to assist them in taking their medications at home.

Pharmacist Bob Eric, owner of Western Hills Pharmacy in Rapid City, SD, provides his elderly clientele with a special medicine container for their weekly medication. The pills are placed in the appropriate time of day and week compartment. The pharmacist from his store will check the elderly individual's container at the end of the week when it is brought to be refilled. This is a very effective way for the elderly to take their medication. Again, by using this on similar dispensers, potential problems can be prevented before a serious injury can occur.

I would like to submit some questions for the record. I must leave shortly. I serve on five committees here in the Senate. Unfortunately my schedule is tight this morning: I am also attempting to get off for a trip to my home State later today.

I do have a question for each of you.

John, do you have further questions that you wish to——

Senator HEINZ. No.

Senator PRESSLER. All right. Then I will ask one question, if I may. Doctor Avorn, how can we better train a physician to reduce an appropriate prescription to the elderly? Do you think the current medical education is responsible for the problem of excessive, inappropriate prescribing. And what changes in curriculum could reduce this problem?

Dr. AVORN. Yes. I do think that we are not educating physicians adequately at present. While there are some things we can try to do for those that are out of the pipeline, we are generating new physicians every year who don't know enough about this area.

I think a nice example is what the Nation has done around geriatrics, in general. We have realized that this is an area of enormous importance, about which physicians are not well-trained.

The Department of Health and Human Services has moved on several fronts to create a variety of modalities to get doctors up to speed on geriatrics in general, which could serve as a very useful model of something that has worked that we can do for geriatric pharmacology.

Specifically, there are geriatric education centers of the sort that Senator Domenici mentioned. We have one in Boston. They are all around the country. They have the mission of disseminating this information and are supported by the Department of Health and Human Services.

There are training grants through the various institutes of NIH—the National Institute on Aging is a prime example—in which people are funded in order to do training of physicians in aging. We could do some of that in aging and pharmacology.

In the private sector front, the Merck Company has taken a leadership role in supporting the creation of fellowships in geriatric pharmacology, which now are in existence in a couple of institutions around the country, to generate the cadre of people who are supposed to go out and teach the teachers of the teachers. That is another step. We needn't assume that government needs to do everything.

Thus, there are precedents in geriatrics about how to get a nation up to speed on something it hasn't really thought about until very recently. We might learn from that and apply it to drugs and the elderly very effectively.

This doesn't really help us with the doctors who are already in practice, but similar approaches might work for them, as well.

Senator PRESSLER. Dr. Simonson, we talk about the important role of the physician in reducing the adverse drug reactions. Tell us about the pharmacist's specific role in reducing drug noncompliance. Do you feel that the Federal Government will have to step in with regulations? What is your solution?

Dr. SIMONSON. On the issue of compliance or improper patient compliance, a survey that I did of pharmacists, the number two most commonly reported problem by pharmacists was patient compliance.

The blister pack that you held up is one very good example of helping patients to comply and helping them to take their medications properly at home, and ideally keep them out of hospitals and nursing homes.

Pharmacy education, itself, has been addressing the needs. One example is in Senator Heinz' state. The Philadelphia College of Pharmacy just started a geriatric pharmacy institute which is designed not just for research, but to help educate pharmacists in a lot of these areas.

In my opinion geriatrics, by definition, is interdisciplinary. I am not a prescriber. I am a pharmacist. But I have a certain expertise in pharmacotherapy that, in working with physicians, we can come up with the best therapy for the patient.

There are regulations now and conditions of participation in long-term care facilities for a pharmacist's monthly review. Generally that has had a very good impact on decreasing improper prescribing. It hasn't solved the problems, as we heard earlier. But compared to two decades ago, things are a lot better.

So there are positive steps being taken by the profession and by education.

Dr. Avorn. If I might make one additional comment. There is always a concern of who is going to pay for this and if it is yet another expenditure. Yet we have heard ample evidence this morning that we are wasting so much money on the consequences of bad prescribing.

On top of that, good prescribing can be so cost-effective in reducing illness that it really is remarkably short-sighted for us to worry, if we do, that this we don't want to spend money on misprescribing because we don't have enough money to do the things we are already doing.

If we had effective programs to improve prescribing for the elderly—in both the Federal and private sectors—we would be reducing a great deal of expenditure, as well as of human suffering, from the consequences of drug under-use, over-use, and mis-use.

Senator Pressler. Well, as one who is addicted to morning coffee and ice cream early in the day, I can see how you can get hooked on over-the counter medications. I take allergy tablets during certain seasons of the year. You can easily become addicted and dependent on allergy tablets. You may have to increase your dose to obtain relief. So adverse drug reaction can occur in all age groups. But I can see how it could be a particular problem for the elderly.

Is American society becoming—aside from the elderly—oriented toward taking medication for everything. I cite allergies as an example. Do people really start depending on these medications?

Is this a problem throughout our society, aside from the elderly? Or not particularly?

Dr. Avorn. There is a sense that there is a pill for every ill, and that whatever bothers you there must be some chemical to make you feel better.

At the same time, we have also got a great number of drugs that we didn't have 10 years ago that are absolutely wonderful for what ails you.

It is a kind of contention between—and the elderly, in particular—the patient feeling as if there must be something to make them feel better and the doctor wanting to comply with that and to pick the drug where we really can help, but not to pick a drug like a sleeping pill or an anti-depressant or a tranquilizer that is trying to treat with chemicals what is fundamentally a problem of somebody's life. That doesn't get better with chemicals.

Senator **Pressler**. Mr. Chairman, I have a couple of extra questions for the record. I wish to submit my statement for the record.

I want to thank our witnesses and staff who have worked on this hearing. I think adverse drug reaction is a very important topic to address.

Senator **Heinz**. Senator Pressler, without objection your questions will be submitted. The responses will appear in the record.

[The prepared statement and questions of Senator Pressler follow:]

STATEMENT OF SENATOR LARRY PRESSLER
before the
Senate Special Committee on Aging
Hearing on

ADVERSE DRUG REACTIONS AND THEIR IMPACT ON THE ELDERLY

MARCH 25, 1988

MR. PRESSLER: MR. CHAIRMAN, I COMMEND YOU AND YOUR STAFF FOR ORGANIZING THIS VERY IMPORTANT HEARING. THE TOPIC OF ADVERSE DRUG REACTIONS (ADRs) AND THEIR DEVASTATING IMPACT ON HUNDREDS OF THOUSANDS OF OUR OLDER CITIZENS IS TIMELY AND APPROPRIATE. UNNECESSARY ADMISSIONS TO HOSPITALS, AND IN SOME CASES DEATH, ARE THE RESULT OF ADRs. THIS NATIONAL TRAGEDY EASILY CAN BE PREVENTED. PUBLIC AWARENESS PROGRAMS DIRECTED TO THE ELDERLY, PHYSICIANS, PHARMACISTS, AND OTHER HEALTH CARE PROVIDERS CAN BE A FOUNDATION TO LAUNCH OUR RESPONSE TO THIS SERIOUS PROBLEM.

IN JUST FORTY YEARS, THERE HAS BEEN AN EXPLOSION IN THE NUMBER OF NEW DRUGS AND TECHNOLOGY ASSOCIATED WITH DRUG RESEARCH IN THE UNITED STATES. THERE ARE WELL OVER 8,000 PRESCRIPTION DRUGS OR COMBINATIONS OF DRUGS AVAILABLE IN OUR COUNTRY.

THE AVAILABILITY OF MEDICATIONS TO REDUCE THE DEVASTATING IMPACT OF DISEASE AND DISABILITY HAS BEEN A GREAT BLESSING TO 30 MILLION AMERICANS WHO ARE 65 YEARS AND OLDER. THESE INDIVIDUALS PURCHASE 30 PERCENT OF ALL DRUGS PRESCRIBED IN THE UNITED STATES. ON AVERAGE, THEY OBTAIN MORE THAN TWICE AS MANY PRESCRIPTIONS AS THOSE UNDER THE AGE OF 65. IT IS ESTIMATED THAT BY THE YEAR 2000 THERE WILL BE 35 MILLION OLDER PEOPLE WHO WILL CONSUME 50 PERCENT OF ALL PRESCRIPTION DRUGS.

BUT, THIS BLESSING BROUGHT ABOUT BY MEDICAL AND PHARMACEUTICAL RESEARCH CAN QUICKLY BECOME A TERRIBLE CURSE TO OUR OLDER POPULATION. ACCORDING TO ASSISTANT SECRETARY FOR HEALTH ROBERT E. WINDOM, THERE ARE ONE MILLION ADDICTS TAKING ILLEGAL DRUGS, BUT THERE ARE 30 MILLION OLDER AMERICANS INTENTIONALLY AND UNINTENTIONALLY MISUSING DRUGS LEGALLY PRESCRIBED BY HEALTH CARE PROFESSIONALS.

INTENTIONALLY AND UNINTENTIONALLY MISUSING MEDICATIONS CAN RESULT IN ADRs. THE U.S. GENERAL ACCOUNTING OFFICE REPORTS THAT 40 PERCENT OF THOSE SUFFERING FROM ADRs ARE OVER AGE 60. ADRs IN PERSONS AGED 60 TO 70 OCCUR AT TWICE THE RATE OF THOSE AGED 30 TO 40, AND SEVEN TIMES MORE OFTEN IN INDIVIDUALS AGED 70 TO 79 THAN IN THOSE AGED 29.

HOWEVER, STATISTICS MAY NOT BE A GOOD GAUGE FOR US TO DETERMINE THE EXTENT OF THIS TERRIBLE PROBLEM. THE NUMBER OF ADRs MAY BE UNDER-REPORTED BECAUSE PHYSICIANS MAY NOT NOTICE THE REACTION OR MAY JUDGE IT TO BE UNRELATED TO THE MEDICAL CONDITION OF THE ELDERLY PATIENT. IN SOME CASES, A PHYSICIAN MAY CHOOSE NOT TO REPORT IT BECAUSE OF FEAR OF A LAWSUIT.

NONCOMPLIANCE IN FOLLOWING A MEDICAL REGIMEN CAN SERIOUSLY HARM THE OLDER ADULT. EXCESSIVE AND INAPPROPRIATE PRESCRIBING MAY EXPOSE THE ELDERLY TO UNNECESSARY PAIN, AND SUFFERING. UNDERMEDICATION CAN LEAD TO INADEQUATE TREATMENT AND INCREASED SEVERITY OF DISEASE. OVERMEDICATION CAN LEAD TO INCREASED HOSPITAL ADMISSIONS AND IN SOME CASES DEATH. MORE THAN 20 PERCENT OF NURSING HOME ADMISSIONS ARE DUE TO THE INABILITY TO MANAGE DRUGS PROPERLY.

NONCOMPLIANCE CAN ALSO BE A RESULT OF POOR COMMUNICATION BETWEEN THE ELDERLY PATIENT AND THE HEALTH CARE PROFESSIONAL. MANY OLDER INDIVIDUALS DO NOT UNDERSTAND THE INSTRUCTIONS GIVEN TO THEM BY THEIR PHYSICIAN. SOME MAY NOT ASK QUESTIONS TO BETTER UNDERSTAND THE INSTRUCTIONS BECAUSE THEY FEEL INTIMIDATED. OTHERS MAY NOT HEAR THE INSTRUCTION GIVEN TO THEM BY THEIR PHYSICIAN DUE TO POOR HEARING.

HEALTH CARE PROVIDERS MUST EQUALLY SHARE THE BLAME FOR NONCOMPLIANCE. SOME ELDERLY SAY THAT THEY RECEIVE LITTLE OR NO INFORMATION ABOUT EITHER THE SIDE EFFECTS OR THE CONTRAINDICATIONS OF THE MEDICATION FROM THEIR PHYSICIAN OR PHARMACISTS.

EVEN WITH ADDITIONAL SUPPORT OF A HOME HEALTH CARE NURSE, THE ELDERLY CONTINUE TO HAVE MEDICATION ERROR PROBLEMS. ONE HOME HEALTH CARE NURSE COMMENTED THAT THERE IS NOT ENOUGH PRINTED LITERATURE WRITTEN IN SIMPLE ENGLISH TO PROVIDE THE OLDER PATIENT WITH ADEQUATE INFORMATION ABOUT DRUG SIDE EFFECTS AND MEDICATION ERRORS. SHE MUST READ THE PHYSICIANS DESK REFERENCE TO DETERMINE THE SIDE EFFECTS OF HER ELDERLY PATIENT'S MEDICATION. THE PATIENT IS GIVEN A HANDWRITTEN PIECE OF PAPER WHICH MAY BE LATER MISPLACED OR LOST.

INAPPROPRIATE PRESCRIBING OF MEDICINE IS A RESULT OF THE ELDERLY POPULATION'S HETEROGENEITY. DRUG ACTION CAN VARY WIDELY IN DIFFERENT OLDER PEOPLE WITH DIFFERENT COMBINATIONS OF DISEASE AND TREATMENTS. SOME OLDER ADULTS HAVE METABOLIC FUNCTIONS SIMILAR TO THOSE OF YOUNGER PEOPLE.

NONCOMPLIANCE CAN OCCUR WHEN THE ELDERLY TAKE MORE THAN ONE PRESCRIPTION DRUG AT THE SAME TIME TO CONTROL MULTIPLE CHRONIC CONDITIONS. FOR EXAMPLE, IN ONE STUDY, OLDER WOMEN TOOK AN AVERAGE OF 5.7 PRESCRIPTION DRUGS AND 3.2 OVER-THE-COUNTER DRUGS AT THE SAME TIME.

TAKING A LARGE NUMBER OF PILLS THAT ARE IN MOST CASES DIFFERENT SIZES, SHAPES, AND COLORS CAN BE CONFUSING TO THE ELDERLY. DIFFERENT DOSAGE SCHEDULES CAN INCREASE THE PROBABILITY OF ERROR IN TAKING THE MEDICATION AT THE WRONG TIME. COMBINING PRESCRIPTION DRUGS AND OVER-THE-COUNTER DRUGS CAN RESULT IN ADRs, NOT TO MENTION FOOD-DRUG INTERACTIONS.

MULTIPLE CHRONIC ILLNESSES THAT OCCUR IN OLD AGE CAN FORCE THE ELDERLY PATIENT TO VISIT NUMEROUS MEDICAL SPECIALISTS WHO UNKNOWINGLY PRESCRIBE MEDICATIONS THAT EITHER COUNTERACT THE BENEFITS OF A MEDICATION ORDERED BY ANOTHER PHYSICIAN OR INTERACT ADVERSELY WITH OTHER PRESCRIBED MEDICATIONS. LACK OF COMMUNICATION BETWEEN THESE SPECIALISTS COMPOUNDED BY AUTOMATIC REFILLS OF MEDICATION CAN FURTHER INCREASE THE ADVERSE EFFECTS OF MEDICATION.

IT IS TIME TO MOVE TO REDUCE THE HIGH INCIDENCE OF ADRs. EDUCATING HEALTH CARE PROVIDERS AND INCREASING AWARENESS OF THIS PROBLEM CAN SURELY BE CONSIDERED A STEP IN THE RIGHT DIRECTION. WE CAN ALSO UTILIZE OTHER WAYS TO ATTACK THIS PROBLEM.

THE FEDERAL DRUG ADMINISTRATION (FDA) MUST BECOME MORE SENSITIVE TO THE NEEDS OF THE ELDERLY. MANY OF THE FDA-APPROVED DRUG LABELS WHICH ADVISE PHYSICIANS, PHARMACISTS AND OTHER HEALTH CARE PROVIDERS ARE INADEQUATE. THEY DO NOT ADDRESS SPECIAL NEEDS OF THE FRAIL ELDERLY POPULATION. IT IS TIME FOR THE FDA TO CONSIDER SPECIAL LABELING THAT WOULD CONTAIN SPECIFIC WARNINGS AND PRECAUTIONS TO THE ELDERLY.

LABELING AND PACKAGING OF PRESCRIPTIONS SHOULD TAKE INTO ACCOUNT THE VISUAL IMPAIRMENT OF MANY OF THE ELDERLY. WHY NOT PROVIDE THE ELDERLY READER WITH LARGE TYPE EASY TO READ INSTRUCTIONS THAT ARE PRINTED WITH COLORS THAT ARE EASY TO SEE?

AREA AGENCIES ON AGING, STATE UNITS ON AGING, SENIOR CENTERS, DAY CARE CENTERS, AND LOCAL COMMUNITY ORGANIZATIONS ACROSS THE COUNTRY COULD BE ACTIVELY INVOLVED WITH "BROWN BAG" PROGRAMS. IN SUCH A PROGRAM, PHYSICIANS AND PHARMACISTS VOLUNTEER THEIR TIME TO EXAMINE THE MEDICATIONS BROUGHT TO THEM IN BROWN LUNCH BAGS BY THE ELDERLY. POTENTIAL PROBLEMS COULD BE DETECTED EARLY.

NEW TECHNOLOGY AND USER FRIENDLY DEVICES COULD BE USED TO ASSIST THE ELDERLY IN TAKING THEIR MEDICATION WHEN THEY RESIDE AT HOME IN THE COMMUNITY. PHARMACIST BOB EHRKE, OWNER OF WESTERN HILLS PHARMACY IN RAPID CITY, SOUTH DAKOTA PROVIDES A VERY IMPORTANT SERVICE TO HIS ELDERLY CLIENTELE. HE PROVIDES THEM WITH A SPECIAL MEDICINE CONTAINER FOR THEIR WEEKLY MEDICATION. PILLS ARE PLACED IN THE APPROPRIATE TIME OF DAY AND DAY OF WEEK COMPARTMENT. A PHARMACIST WILL CHECK THEIR CONTAINER AT THE END OF THE WEEK WHEN IT IS BROUGHT IN TO BE REFILLED. AGAIN, POTENTIAL PROBLEMS CAN BE DETECTED BEFORE SERIOUS INJURY CAN OCCUR.

DRUG THERAPY PROGRAMS TO REDUCE THE AMOUNT OF DRUGS TAKEN BY THE ELDERLY IN NURSING HOMES AND IN THE COMMUNITY COULD BE ENCOURAGED BY THE FEDERAL GOVERNMENT THROUGH FUNDING OF PILOT PROJECTS AND EDUCATION PROGRAMS.

MR. CHAIRMAN. I APPRECIATE THIS OPPORTUNITY TO PRESENT MY VIEWS ON THIS PROBLEM. WE CAN CONFRONT THE PROBLEM EASILY WITH THE HELP OF PHYSICIANS, PHARMACISTS, NURSES, AND THE ELDERLY THEMSELVES.

Senator **Heinz**. I have no further questions for our witnesses. I thank them all.

I thank the staff on both sides for their hard work in preparing for this hearing, and for Senator Melcher for scheduling it.

The hearing is adjourned.

[Whereupon, at 12:20 p.m., the committee was adjourned.]

APPENDIXES

APPENDIX 1

CORRESPONDENCE BETWEEN THE COMMITTEE AND THE FOOD AND DRUG ADMINISTRATION

Item 1

JOHN MELCHER, MONTANA, CHAIRMAN

JOHN GLENN, OHIO	JOHN HEINZ, PENNSYLVANIA
LAWTON CHILES, FLORIDA	WILLIAM S. COHEN, MAINE
DAVID PRYOR, ARKANSAS	LARRY PRESSLER, SOUTH DAKOTA
BILL BRADLEY, NEW JERSEY	CHARLES E. GRASSLEY, IOWA
QUENTIN N. BURDICK, NORTH DAKOTA	PETE WILSON, CALIFORNIA
J. BENNETT JOHNSTON, LOUISIANA	PETE V. DOMENICI, NEW MEXICO
JOHN B. BREAUX, LOUISIANA	JOHN H. CHAFEE, RHODE ISLAND
RICHARD SHELBY, ALABAMA	DAVE DURENBERGER, MINNESOTA
HARRY REID, NEVADA	ALAN K. SIMPSON, WYOMING

MAX I. RICHTMAN, STAFF DIRECTOR
G. LAWRENCE ATKINS, MINORITY STAFF DIRECTOR

United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

March 15, 1988

The Honorable Frank Young, M.D.
Commissioner
Food and Drug Administration
Department of Health and
  Human Services
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Young:

As Chairman of the Special Committee on Aging, I am requesting that you appear before the Committee on March 25, 1988 at 9:30 a.m. to testify on the FDA's approval processes for drug labeling and new drug applications as these processes relate to safety and efficacy of drugs prescribed for older Americans.

The Committee would very much appreciate your addressing the following issues:

1. What steps has the FDA taken to protect the elderly population from needless and preventable adverse reactions and interactions associated with prescription drugs?

2. What additional steps does the FDA intend to, or would like to, pursue toward better protecting elders from needless, preventable, and sometimes dangerous, adverse reactions and interactions associated with prescription drugs?

3. Why do not the FDA-approved labels for most prescription drugs heavily used by the elderly contain specific sections for indications/contraindications and precautionary/warning statements for "use in elderly patients"; and should these labels contain such sections for the elderly similar to those that are found concerning infants/children and pregnancy?

4. Why has the FDA failed to finalize and publish its five-year-old draft "Guidelines For Clinical Testing Of Drugs In The Elderly"?

5. Has the FDA conducted or funded in the past six years descriptive and/or analytic epidemiologic studies into the frequency, causality or any other aspect associated with adverse drug reactions and interactions in the elderly? If so, please provide a listing of these studies, a description of each, the cost(s), and mode(s) of funding?

The Committee would be glad to receive your thoughts and views on any other issues which you believe are important regarding the labeling and new drug application processes as they affect the elderly.

Please provide the Committee with ten copies of your testimony by close of business on March 23, 1988, and an additional 100 copies on the morning of March 24, 1988. Your prepared statement for inclusion in the record may be whatever length you deem appropriate. We would appreciate your limiting your oral presentation before the Committee to approximately five minutes in order to provide time for questions from the Members.

Should you have any questions regarding the hearing, please have your staff contact Max Richtman, Staff Director for the Committee, at 224-5364.

Thank you for your cooperation and assistance in this important matter.

Sincerely,

John Melcher

JOHN MELCHER
Chairman

JM:jfm

Item 2

JOHN MELCHER, MONTANA, CHAIRMAN
JOHN GLENN, OHIO
LAWTON CHILES, FLORIDA
DAVID PRYOR, ARKANSAS
BILL BRADLEY, NEW JERSEY
QUENTIN N. BURDICK, NORTH DAKOTA
J. BENNETT JOHNSTON, LOUISIANA
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ALAN K. SIMPSON, WYOMING
MAX I. RICHTMAN, STAFF DIRECTOR
G. LAWRENCE ATKINS, MINORITY STAFF DIRECTOR

United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

March 30, 1988

The Honorable Frank Young, M.D.
Commissioner
Food and Drug Administration
Department of Health and
Human Services
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Young:

As you know, the Committee conducted a hearing on March 25, 1988 concerning "Adverse Drug Reactions: Are Safeguards Adequate For The Elderly?". We regret that you were unable to attend the hearing and share with us your thoughts and views regarding this important issue.

Testimony of researchers, health care providers and victims of preventable adverse drug reactions made it all too clear that there is, indeed, a critical need for systematic clinical testing of new drugs in the elderly, as well as more complete and up-to-date information specifically concerning the elderly in FDA-approved drug labeling for physicians and other health care providers.

Because you were unable to testify, we are requesting that you inform us no later than April 15, 1988 of the exact date by which the FDA intends to finalize and publish its five-year-old draft "Guidelines For Clinical Testing Of Drugs In The Elderly." We are also requesting that you explain why the FDA does not require, where appropriate, a specific section titled: "For Use In The Elderly" in drug labeling, since a similar section is required for infants/children and pregnant women.

Should you have any questions regarding these requests, please have your staff contact Max Richtman, Staff Director for the Committee, at 224-5364.

Thank you for your cooperation and assistance in this important matter.

Sincerely,

John Melcher
JOHN MELCHER
Chairman

JOHN HEINZ
Ranking Minority
Member

Item 3

Jim M.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 15 1988

The Honorable John Melcher
Chairman, Special Committee on Aging
United States Senate
Washington, D.C. 20510-8400

Dear Mr. Chairman:

Subsequent to your March 25, 1988, hearing on drugs and the elderly, in a letter dated March 30, 1988, you wrote to Dr. Frank E. Young, Commissioner, Food and Drug Administration, and requested that he provide the Committee by April 15, 1988, certain information on clinical guidelines and labeling with respect to the elderly.

I regret to say that the response to your letter will be delayed until early May and hope that this will not inconvenience the Committee. Please accept my apologies. Meanwhile, we are continuing to provide documents to the Committee in response to previous requests.

We are sending a similar letter to Senator Heinz.

Sincerely yours,

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

Item 4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

March 23, 1988

The Honorable John Melcher
Chairman, Special Committee on Aging
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

I write to respond to your letter of March 15, inviting me to testify on March 25, 1988 before the Committee on FDA's activities related to the safety and effectiveness of drugs prescribed for older Americans. I appreciate your understanding of why we are unable to accept as we discussed with your staff. The significant and complex nature of this issue requires that we allow adequate time to prepare so that we might provide you with information that is both meaningful and complete.

I assure you that the Agency continues to play an active role in improving the use of drugs in older Americans. Enclosed is a brief description of our activities.

If you would like any additional information to be submitted for the hearing record, please let me know.

Sincerely yours,

Frank E. Young

Frank E. Young, M.D., Ph.D.
Commissioner of Food and Drugs

FDA's Activities Related to Drugs Prescribed for Older Americans

We have been increasing our knowledge of the effects of drugs in this age group by encouraging the participation of older subjects in the testing of drugs and will soon finalize guidelines for premarket testing of drugs in the elderly. Although these guidelines are still in draft form, they have had a major impact in providing discussion of innovative ways to determine all of the factors, such as age, that can influence drug pharmacokinetics. The guidelines are already being implemented in that the pharmaceutical industry is utilizing them. In addition, we have published a proposed Guideline for the Format and Content of the Clinical Data Section of a New Drug Application which emphasizes the need to analyze data to search for any relationship of both favorable and unfavorable responses to age, and to conditions common in older patients, including abnormal kidney function, multiple diseases and drug therapy. Furthermore, FDA provides Institutional Review Board (IRB) education through workshops and the dissemination of information sheets to ensure that premarket testing adequately considers the needs of older people. An IRB governs the review and conduct of all human research at a particular institution involving products regulated by FDA.

In addition, we now have more knowledge regarding the effects of drugs in older Americans through post-marketing surveillance monitoring which is primarily based on adverse drug reaction reports generally submitted by the practicing physician. The purpose of surveillance monitoring is to provide new information of drug risks that can be used for modifications in drug usage.

FDA has also been involved in interagency cooperative efforts relating to the health needs of older Americans, including the area of medications. One example of this is the "Surgeon General's Workshop - Health Promotion and the Aging," which is taking place this week. Under the direction of the Surgeon General, FDA has taken a major lead in the staffing, planning and execution of this workshop. The workshop will use invited experts to consider aging issues and develop a set of recommendations that will serve as the core for the Public Health Service efforts. FDA is coordinating the worksession entitled "Medications and Geriatrics." Attached is a copy of the work paper that is being used at this session.

Another FDA activity for improving the use of drugs by older Americans is in patient education. FDA has had a long tradition of working with major national and community-based organizations to develop programs and materials to advance public health goals to improve the health status of older citizens. During the last six years the Agency has been coordinating the development and implementation of significant patient education programs with the National Council on Patient Information and Education (NCPIE) which is a nongovernmental group of some 240 health organizations. FDA and NCPIE sponsored the "Get the Answers" campaign which is a program urging patients to ask their health professionals questions about their prescriptions. The major component of the campaign is a medical data wallet card that lists the five questions patients should ask when they get a prescription. The "Get the Answers" message has been widely disseminated to consumers through news releases, advice columns, and other media. NCPIE commissioned a report, released in October 1987, "Priorities and Approaches for Improving Prescription Medicine Use by Older Consumers" and this past year sponsored a campaign to improve the use of prescription medicine by older consumers.

Other educational initiatives undertaken by the Agency, in conjunction with national organizations, include national conferences addressing areas of importance to older women and educational programs in such areas as health fraud, tamper-resistant packaging efforts, and osteoporosis. Attached is a list of activities that have been undertaken by FDA and national organizations to respond to educational needs of the elderly.

In 1985, FDA's Center for Drug Evaluation and Research (then the Center for Drugs and Biologics), disseminated a newspaper column entitled "Safety Sense" to weekly suburban newspapers nationwide through North American Precis Syndicate, Inc. This column provided specific information for older Americans to ensure their safe and proper use of medications.

In addition, FDA publishes materials and conducts meetings across the Nation to address issues affecting the elderly population including drug use in older Americans. Specifically of interest are two articles reprinted from the FDA Consumer magazine, "Medicine and the Elderly" (September 1983), and "Questions About Your Medicine? Go Ahead--Ask" (October 1987). Our activities also include a major campaign to encourage health professionals to provide drug information to their patients.

Moreover, Parke-Davis gave a presentation to FDA on March 9, on the firm's Elder-Care program. This program, which is directed to the elderly, provides basic information on drugs, drug-taking, drug reactions, and drug contraindications. We are now considering the utility of incorporating some of the Parke-Davis materials into programs for the elderly. In fact FDA intends to make drug information for the elderly a major priority for the Agency in its Action Plan Phase III.

Attachments

FDA/National Organization Educational Initiatives

The Food and Drug Administration has had a long tradition of working with major national and community-based organizations to develop programs and materials to advance priority public health goals to improve the health status of older Americans. Many of the issues and educational initiatives undertaken by the Agency address the health and welfare of older citizens including tamper-resistant packaging efforts, the development of clinical guidelines for drug testing in the elderly, national conferences addressing areas of importance to older women, and key educational programs in such areas as health fraud, patient education, sodium reduction, and osteoporosis.

Specifically, the following are examples of the many activities that have been taken by FDA and national organizations to respond to the health information and education needs of the elderly:

FDA/American Association for Retired Persons cooperative projects have included joint slide shows on nutrition/sodium reduction and on health fraud; Dr. Young has met with the AARP Executive Board to discuss priorities mutually-shared; and meetings between Dr. Young, top FDA officials, and national organizations including AARP to discuss such issues as tamper-resistant packaging and priorities for the FDA Action Plan.

FDA/National Council of Senior Citizens have worked together to present "train the trainer" programs for the Council's regional/local representatives on patient education on prescription medications and health fraud. The Agency has also presented a workshop at the Council's annual national conference on health fraud and the elderly.

FDA/Auxiliary to the National Medical Association have just recently launched a demonstration project to "train the trainers" in several ANMA regional locations to bring the patient education on prescription drug messages to the Black elderly and their families.

FDA/PHS Coordinating Committee on Women's Health Issues cosponsored the 1986 National Conference on Women's Health which included a separate panel session on the "Contemporary and Emerging Health Concerns for Older Women." In addition, the conference also addressed major conditions of importance to the older woman including osteoporosis, patient education and communication, cancer, and nutrition. The proceedings from this conference were distributed to over 10,000 public health professionals and educators throughout the country.

FDA/Key Agencies in the Public Health Service/National Osteoporosis Foundation sponsored the 1987 FDA Special Topic Conference on Osteoporosis as the first in a series of national fora under the National Conference on Women's Health Program to address the health concerns of women. Proceedings of this conference will be published in PHS Reports and disseminated to over 10,000 public health professionals and educators. The Agency has worked with the National Osteoporosis Foundation to involve the FDA Consumer Affairs Officers located throughout the country in the 1988 National Osteoporosis Prevention Week initiative which is sponsored by Congresswoman Olympia Snow and which will focus prevention messages to the younger, middle-aged, and older woman.

Item 5

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

June 2, 1988

The Honorable John Melcher
Chairman, Special Committee on Aging
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

I am writing in further response to your letter of March 30, 1988, following your March 25 hearing on drugs and the elderly. In your letter you ask when the FDA intends to finalize its "Guidelines for Clinical Testing of Drugs in the Elderly" and why drug labeling is not required to contain, where appropriate, a special section on use of drugs in the elderly similar to the current required sections for pediatric use and use during pregnancy.

Clinical Testing Guidelines

In my letter to you of March 23, 1988, I noted the substantial progress in evaluating drugs in the elderly which has occurred since FDA's 1983 discussion paper on clinical testing of drugs in the elderly. This was not a formally proposed guideline, and our next step will be to publish a formal proposal.

In the interim, FDA published a new draft "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application," which should be published in final form within the next few months. This guideline calls for analysis of the effects of age on both safety and effectiveness. Recent New Drug Applications have already included such analyses, and the guideline is already widely used.

Now that the clinical/statistical guideline is essentially complete, I believe our staff can act on the draft guideline for clinical testing of drugs in the elderly during the next few months. I have asked that the Center for Drug Evaluation and Research complete action on a formally proposed guideline by the end of August 1988.

Drug Labeling

Drug labeling concerning use in the elderly has been under FDA consideration for several years. However, in the past, little information in this area has been available. Data on the use of many drugs in the older population is now sufficiently developed to allow for the inclusion of a meaningful and useful section in the labeling, and I have asked my staff to develop a proposed change in the regulations which would add a section on use in elderly patients.

I share your interest in this matter and while the Agency has not yet produced a final guideline for the study of drugs in the elderly, I believe our 1983 discussion paper was a seminal event in stimulating progress in obtaining better information on how to use drugs safely and effectively in older patients. I assure you that we will continue to make progress in this important area.

We are sending a similar letter to Senator Melcher.

Sincerely yours,

Frank E. Young, MD, Ph.D
Commissioner of Food and Drugs

APPENDIX 2

FOLLOWUP QUESTIONS TO AND ANSWERS FROM WITNESSES

Item 1

JOHN MELCHER, MONTANA, CHAIRMAN

JOHN GLENN, OHIO
LAWTON CHILES, FLORIDA
DAVID PRYOR, ARKANSAS
BILL BRADLEY, NEW JERSEY
QUENTIN N. BURDICK, NORTH DAKOTA
J. BENNETT JOHNSTON, LOUISIANA
JOHN B. BREAUX, LOUISIANA
RICHARD SHELBY, ALABAMA
HARRY REID, NEVADA

JOHN HEINZ, PENNSYLVANIA
WILLIAM S. COHEN, MAINE
LARRY PRESSLER, SOUTH DAKOTA
CHARLES E. GRASSLEY, IOWA
PETE WILSON, CALIFORNIA
PETE V. DOMENICI, NEW MEXICO
JOHN H. CHAFEE, RHODE ISLAND
DAVE DURENBERGER, MINNESOTA
ALAN K. SIMPSON, WYOMING

MAX I. RICHTMAN, STAFF DIRECTOR
G. LAWRENCE ATKINS, MINORITY STAFF DIRECTOR

United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

April 27, 1988

Jerry Avorn, M.D.
Director
Program for Analysis of
Clinical Strategies
Department of Social Medicine
and Health Policy
Harvard Medical School
643 Huntington Ave.
Boston, Mass. 02115

Dear Dr. Avorn:

Thank you for taking the time out of your busy schedule on March 25, 1988 to testify at the Committee's hearing on "Adverse Drug Reactions: Are Safeguards Adequate For The Elderly?". Your excellent testimony very strongly underscored the pressing need to ensure that health care providers are fully aware of the potential dangers of inappropriate and excessive prescribing of drugs for older Americans. For your information, I am enclosing a news reporter's view of the hearing that I thought you might find interesting.

Due to time constraints, Senators Pressler, Grassley, and I were unable to ask a number of questions that we believe are important. Therefore, the Committee would very much appreciate your providing answers to the questions listed below so that we may complete the hearing record.

1. You indicated that you would support the establishment of a much more comprehensive, Department of Health and Human Services funded, demonstration education outreach program for health care providers. Partially as a result of our hearing, some believe that there is sufficient information currently available to go forward now and implement a successful national drug education outreach program. Would you agree with that assessment or do you believe that further demonstration programs are necessary to determine how to most cost effectively and successfully implement such a broad program?

2. If you believe that a demonstration program is still advisable prior to implementing on a national scale, how large a program should this be? Should it begin with a demonstration project and, if so, how many states would you include in such a study?

3. With regard to costs, can you estimate for us the cost of such a demonstration project, and is it possible that this project would realize any financial savings or, at least, pay for itself?

4. If such an education outreach program were to be established nationwide, what do you imagine the potential savings could be to the Medicare and Medicaid programs, as well as to the beneficiaries themselves?

5. During the course of your education outreach studies, what has been your experience as to the willingness of physicians to receive information, suggestions, or advice about the need for special prescribing practices for the elderly population?

6. As to what is available now in the way of information to physicians and other health care providers, is not the Physicians Desk Reference (PDR) relied upon most heavily in drug prescribing; and, if so, is the information contained in this volume adequate to ensure appropriate prescribing of drugs for the elderly?

7. In your testimony, you briefly referred to an ongoing study of medication misuse in nursing homes. What have been your findings to date in this study?

8. Why is there not more testing of drugs in the elderly prior to marketing?

We appreciate your taking the time to answer these questions and will, of course, forward you the final hearing print as soon as it is available. Should you have any questions regarding this request, please contact James Michie of the Committee staff at (202) 224-5364.

Thank you for your cooperation and assistance with this request. We look forward to reviewing your responses.

Best regards.

Sincerely,

John Melcher
Chairman

Enclosure

Item 2

HARVARD MEDICAL SCHOOL

PROGRAM FOR THE ANALYSIS OF CLINICAL STRATEGIES

643 Huntington Avenue
Boston, Massachusetts 02115
(617) 732-1005

July 13, 1988

Senator John Melcher
Chairman, Special Committee on Aging
United States Senate
Room SD-G41
Washington, D.C. 20510-6400

Dear Senator Melcher:

Thank you for the opportunity to testify at the Committe's hearing on adverse drug reactions, and for your kind words concerning my contribution. For the record, I am pleased to respond to the additional questions you submitted to me on behalf of the Chair as well as Sentors Pressler and Grassley. I will attempt to respond to them as best I can in the order in which you presented them in your letter.

1. I agree that the time has come for the creation of a large-scale, comprehensive program through the Department of Health and Human Services to educate physicians about developments in geriatric pharmacology. My own work with Steve Soumerai dating back to the early 1980's has shown that prescribing appropriateness can be approved in a highly cost-effective manner by such a program, which we have shown would actually save more dollars than it costs. (Mr. Michie of your staff has been sent copies of the research papers documentating these findings in some detail.) There is very solid evidence that such a program could begin on a large scale at any time. A phase-in period in which such a program would exist in several states initially might be an appropriate first step to get this off the ground.

2. Such an initial "demonstration" phase would ideally start with about five states. This would provide enough geographic mix and size to make it a meaningful start-up activity, from which important lessons could be learned concerning a national-level program.

3. Dr. Soumerai and I found that in the early 1980's, it was possible to put an experienced clinical pharmacist in the field at a cost of about $90 per physician visited, assuming two twenty-minute educational sessions per physician over a six-month period. The detailed benefit-cost analysis we performed indicated that the savings to the Medicaid programs alone in the four study states were about twice this program cost. Thus, there is reason to believe that such a program could pay for itself from the very start.

4. The study cited above would suggest that depending upon the scale of the effort that was mounted, we can project a savings of approximately $2 for every $1 spent on such an activity. It should be noted that this projection is based on actual data from our four-state pilot study, and is not mere speculation. Thus, the dollar savings could easily run into the millions anually. Of greater importance is the benefit that would be derived by Medicare and Medicaid beneficiaries themselves, who would likely experience

fewer adverse drug reactions, were such a program to succeed. Given the very high cost of care for these patients, this would result in additional economic as well as human benefits from the point of view of medical care costs avoided.

5. In our initial study, we found that 92% of physicians who had been randomly assigned to the "outreach education" group were willing to spend time meeting with our educational staff. These were typical moderate or high prescribing physicians, not volunteers. As the educational program went on, we found a very high level of interest in such consultation on the part of the physicians, who often noted that they had need of an impartial, non-commercial source of up-to-date information about prescribing. With increasing awareness by the public and the medical profession about adverse drug effects in the elderly, this need is growing daily. I am unable to keep up with all of the requests I recieve to lecture groups of interested physicians about the proper use of drugs in the aging patient.

6. It is true that the Physician's Desk Reference (PDR) is relied upon most heavily by prescribing physicians. However, as was amply demonstrated in the Committee's recent hearings, the adequacy of description in the PDR concerning proper medication use in the elderly is very spotty. Considerable progress needs to be made in drug labeling (of which the PDR is a compendium) to address this probem.

7. Since the hearing, my colleagues and I have had the opportunity to analyze further the findings from our study of medication misuse in nursing homes. We have found the frequency of use of sedative medications and other psychoactive substances to be disturbingly high. Even more important, we are finding that the educational outreach program we developed, in which a clinical pharmacist met in person with physicians, nurses, and aides to teach them about geriatric pharmacology, appears to have worked very well. The nursing homes randomized to recieve this information have shown dramatic improvement in the patterns of medication use, and in reduction of excessive ssedation, as compared with similiar homes randomized to the no-intervention group.

8. The elderly have been relatively ignored in pre-marketing studies of drugs because they are felt to be "messier" in the drug testing and data analysis process, in that they are likely to have less adequate liver and kidney function, more co-existing illnesses and other medication use, and are more prone to drug side effects. Therefore, companies have been reluctant to involve in pre-marketing testing any group whose findings ar likely to slow down the process of drug approval. Although the FDA has been talking about imposing guidelines for inclusion of the elderly in this process since 1982, no formal rules have ever been issued.

I hope these answers are of some use to you and other members of the Committee, and I stand ready to help further this important effort in any way that I can. My colleagues and I appreciate the leadership role which the Committee has taken in this pursuing matter, and congratulate on your efforts thus far.

Sincerely,

Jerry Avorn

Jerry Avorn, M.D.
Associate Professor

JA/sb

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Item 3

United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

April 28, 1988

J.W. Colinger, M.D., P.C.
Medical Director
Life Care Center of Erwin
Stalling Lane
Erwin, Tennessee 37650

Dear Dr. Colinger:

Thank you for taking the time out of your busy schedule on March 25, 1988 to testify at the Committee's hearing on "Adverse Drug Reactions: Are Safeguards Adequate For The Elderly?". Your excellent testimony very strongly underscored the pressing need to ensure that health care providers are fully aware of the potential dangers of inappropriate and excessive prescribing of drugs for older Americans.

Due to time constraints, Senators Pressler, Grassley, and I were unable to ask a number of questions that we believe are important. Therefore, the Committee would very much appreciate your providing answers to the questions listed below so that we may complete the hearing record.

1. Are there particular problems in monitoring drug misuse in nursing homes and in keeping track of adverse drug reactions in nursing homes?

2. Why did you feel that it was necessary to institute a drug holiday program at your facility?

3. Did your nursing home administrator, Director of Nurses, and consulting pharmacist develop the program together?

4. Were there any results from your program that you would describe as negative or counterproductive in nature?

5. How can a drug holiday program similar to the one you developed be repicated across the nation? Do you think it would be relatively easy to do?

We appreciate your taking the time to answer these questions and will, of course, forward you the final hearing print as soon as it is available. Should you have any questions regarding this request, please contact James Michie or Christopher Jennings of the Committee staff at (202) 224-5364.

Thank you for your cooperation and assistance with this request. We look forward to reviewing your responses.

Best regards.

Sincerely,

John Melcher
Chairman

Item 4

J. W. Colinger, M.D., P.C.

May 12, 1988

Senator John Melcher
United States Senate
Special Committee on Aging
Washington, DC 20510-0600

Dear Senator Melcher:

Thank you again for the opportunity of testifying at the Committee's hearing of March 25, 1988. I strongly concur that there is an epidemic of inappropriate and excessive prescribing in this nation. Physicians must be accountable for their prescribing patterns regardless of the type of practice. In response to the additional questions submitted in your letter of April 28:

1. *Are there particular problems in monitoring drug misuse in nursing homes and in keeping track of adverse drug reactions in nursing homes?*

   Allied health personnel are not trained to judge what constitutes misuse of or adverse reaction to a specific drug. Physician time and interest in dealing with these problems therefore is critically important if this is to be done successfully. In facilities which have multiple staff physicians there are no clearcut lines of authority that allow another physician to judge the inadequacies of the therapeutic regimen of the attending physician. The facilities' pharmacists can assist certainly in monitoring drug usage but lack the knowledge to judge what constitutes misuse. Regarding adverse drug reaction, some are observable and apparent while others require periodic blood testing in order to monitor.

   Ultimately, I believe what is needed is a federal mandate that drug utilization review become an integral part of nursing home facilities' quality assurance programs. Only with the threat of loss of accreditation or licensure will facilities and staff physicians take the time to undertake the essential task.

2. *Why did you feel that it was necessary to institute a drug holiday program at your facility?*

   There are two basic reasons for all nursing home facilities to implement a drug holiday program for psychotrophic medications. The first is to re-evaluate the necessity for continuation or not of the medication. Secondly, by pro-

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J. W. Colinger, M.D., P.C.

viding a drug free interval, this may reduce the incidence of untoward side effects and adverse drug reactions.

3. Did your nursing home administrator, Director of Nurses, and consulting pharmacist develop the program together?

I developed the drug holiday program. The drug utilization review process was a joint effort on the part of the administration, the director of nursing and myself.

4. Were there any results from your program that you would describe as negative or counterproductive in nature?

Discontinuation of psychotrophic medications in patients with a dementia such as Alzheimer's disease does create problems for our nursing staff and support personnel. These patients wander within the facility and tend to be more hostile than the normal population. It is our philosophy not to chemically or psychically restrain these patients unless they are a threat to themselves or our other patients. Maintaining a patient on a regimen as free as possible from mind altering drugs improves their quality of life. In adopting this philosophy the administration of our facility is choosing improvement in the quality of life of patients over what is expedient for the facility. Higher staffing levels and thus increased cost of personnel are required to allow the patients to live as free as possible from psychotrophic medications.

5. How can a drug holiday program similar to the one you developed be replicated across the nation? Do you think it would be relatively easy to do?

Due to the higher staffing levels required, it may be difficult to convince management that a drug holiday program and the reduction of the use of psychotrophic medications is a good thing. The implementation of the drug holiday program and drug utilization review program is simple to understand in concept but does require diligence in application, concurrent review, and a determination on the part of the facility that each patient's drug treatment regimen is optimal.

Sincerely,
J. W. Colinger M.D.
J.W. Colinger, M.D., P.C.

105 GAY STREET, ERWIN, TN 37650 PHONE 743-6141

Item 5

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

April 27, 1988

William Simonson, Pharm.D.
V.A. Medical Center
P.O. Box 1034
Portland, Oregon 97207

Dear Dr. Simonson:

Thank you for taking the time out of your busy schedule on March 25, 1988 to testify at the Committee's hearing on "Adverse Drug Reactions: Are Safeguards Adequate For The Elderly?". Your excellent testimony very strongly underscored the pressing need to ensure that health care providers are fully aware of the potential dangers of inappropriate and excessive prescribing of drugs for older Americans. For your information, I am enclosing a news reporter's view of the hearing that I thought you might find interesting.

Due to time constraints, Senators Pressler, Grassley, and I were unable to ask a number of questions that we believe are important. Therefore, the Committee would very much appreciate your providing answers to the questions listed below so that we may complete the hearing record.

1. We talk about the important role of the physician in reducing adverse drug reactions. What should the pharmacist's role be in reducing drug noncompliance, and what do you believe should be the federal government's role in reducing adverse drug reactions?

2. Is the problem older people experience with multiple drug interactions ultimately a problem of lack of research and knowledge on the problem, or failure to educate and train physicians and pharmacists about drug interactions, or is it some combination of both?

3. Are there particular problems in monitoring drug misuse in nursing homes and in keeping track of adverse drug reactions in nursing homes?

4. You indicated that you would support the establishment of a much more comprehensive, Department of Health and Human Services funded, demonstration education outreach program for health care providers. Partially as a result of our hearing, some believe that there is sufficient information currently

available to go forward now and implement a successful national drug education outreach program. Would you agree with that assessment or do you believe that further demonstration programs are necessary to determine how to most cost effectively and successfully implement such a broad program?

5. You wondered in your statement how many elderly people have been sentenced to a life of institutionalized chemical restraint because they manifested adverse drug reactions which were misdiagnosed as mental illness or diseases of old age. Is there any kind of empirical data on that question? I believe such information would not only help prevent that kind of situation, assuming they exist, but could well save lives through some sort of intervention. If such information isn't available, do you have any suggestions as to how we could obtain it?

6. How serious is the problem of poor patient compliance, especially as it pertains to the use of non-prescription, over-the-counter medications taken while an individual was also taking prescribed medication?

7. In your testimony, you briefly referred to an ongoing study of medication misuse in nursing homes. What have been your findings to date in this study?

8. Why is there not more testing of drugs in the elderly prior to marketing?

We appreciate your taking the time to answer these questions and will, of course, forward you the final hearing print as soon as it is available. Should you have any questions regarding this request, please contact James Michie or Christopher Jennings of the Committee staff at (202) 224-5364.

Thank you for your cooperation and assistance with this request. We look forward to reviewing your responses.

Best regards.

Sincerely,

John Melcher
Chairman

Enclosure

Item 6

College of Pharmacy Oregon State University Corvallis, Oregon 97331-3507 (503) 754-3725

July 19, 1988

Senator John Melcher, Chairman
U.S. Senate Special Committee on Aging
SD G-41 Dirksen Building
Washington, D.C. 20510

Dear Senator Melcher,

Thank you for sending me the follow-up questions from your committee's March 25, 1988 hearing on Adverse Drug Reactions in the Elderly. I have answered these questions to the best of my ability and have provided my responses below.

Question 1. We talk about the important role of the physician in reducing adverse drug reactions. What should the pharmacist's role be in reducing drug noncompliance, and what do you believe should be the federal government's role in reducing adverse drug reactions?

Response: The role of the pharmacist is rapidly evolving from one that was almost entirely related to control of the drug product, to one that stresses the professional role of the pharmacist as an educator and a provider of information. Pharmacists routinely educate patients concerning what their medications are for, how they work, what to expect when taking them, what side effects might occur and how to take medications properly. It has been demonstrated that when patients understand their medications, they are more likely to take them appropriately and less likely to experience adverse reactions due to inappropriate use. In addition, when patients are aware of likely or serious potential adverse drug reactions they are more likely to recognize their medications as the cause of these adverse effects. If and when adverse drug reactions do occur the proper interventions such as stopping the medication and contacting the physician can be implemented. This reduces the chance that the adverse reaction will progress to a more serious medical problem, or even a hospital or nursing home admission.

A number of innovative pharmacists are also implementing a variety of compliance encouraging techniques such as dispensing medications in easy to read and open "calendar packs" as well as sending prescription refill reminders to patients. Interventions such as these can have a significant favorable impact on patient compliance.

I believe that the Federal government can assist in reducing adverse drug reactions by encouraging an environment where pharmacists can implement these innovations and where they are encouraged to serve in their role as patient educators. This can best be done by developing reimbursement mechanisms which allow pharmacists to be paid for their knowledge and their professional services rather than the current system where reimbursement is directly tied to the provision of drug product. Existing reimbursement mechanisms reward pharmacists when they fill a prescription. The incentive is clearly for the pharmacist to sell more medications. As we discussed in the hearing it is often more appropriate to reduce medication use in the elderly rather than increase it. It seems wise to uncouple pharmacist reimbursement from the drug product at least in some situations. This would then provide the incentive for pharmacists to discourage inappropriate medication consumption. It would also encourage pharmacists to work in settings such as home health care agencies, outpatient clinics and senior citizen centers to identify medication problems such as adverse drug reactions. This would allow proper intervention before serious problems and/or institutionalization occur. If the incidence of institutionalization due to adverse drug reactions could be reduced by even one percent such a program would easily pay for itself while at the same time increasing the quality of life of elderly consumers of medications.

Question 2. Is the problem older people experience with multiple drug interactions ultimately a problem of lack of research and knowledge on the problem, or failure to educate and train physicians and pharmacists about drug interactions, or is it some combination of both?

Response: It is probably a combination of both. There is a relative lack of research performed in elderly subjects even though there has been a significant increase in geriatric research in recent years. There is also a lack of training in geriatrics across all health professions. In a recently published study of geriatric coursework offered by all 72 Pharmacy schools in the United States, I and a colleague determined that it is possible to graduate from 19 schools of pharmacy with no exposure to geriatrics. We also determined that only 9 schools require all pharmacy students to complete courses that deal primarily with geriatrics. (Pratt, Simonson & Boehne. Gerontology & Geriatrics Education 1987;7:17-27) Efforts are being made to increase these geriatric offerings but curricular changes often take a great deal of time.

Question 3. Are there particular problems in monitoring drug misuse in nursing homes and in keeping track of adverse drug reactions in nursing homes?

Response: Problems with inappropriate drug use in nursing homes certainly do exist, however it is actually easier to monitor for drug misuse and adverse drug reactions in the nursing home than it is in the community. Patients are routinely observed in nursing homes and detailed patient records are kept. This enables staff to document changes in a patient's condition which could be the result of adverse drug reactions. In the nursing home detailed medication records are kept and every dose of medication that is administered is recorded.

Since 1974 Conditions for Participation of skilled nursing facilities in Medicare/Medicaid have required pharmacists to conduct a monthly review of drug therapy. This requirement has recently been extended to include all patients in intermediate care facilities. The success of pharmacist conducted drug therapy review has been documented through a decrease in inappropriate drug use in nursing homes. The next logical step is to expand this requirement to other areas of patient care where medication misuse is common. These environments include those settings where medication monitoring by the pharmacist is not required such as adult foster care and home health care. Undoubtedly there are many patients in these and other settings that are experiencing preventable and reversible problems with their medications.

Question 4 . You indicated that you would support the establishment of a much more comprehensive, Department of Health and Human Services funded, demonstration education outreach program for health care providers. Partially as a result of our hearing, some believe that there is sufficient information currently available to go forward now and implement a successful national drug education outreach program. Would you agree with that assessment or do you believe that further demonstration programs are necessary to determine how to most cost effectively and successfully implement such a broad program?

Response: Considerable work has been done in the area of drug education within the different disciplines, so the components of a good drug education outreach system already exist. How these components can best be integrated to benefit the elderly patient has yet to be determined however. I support the development of a HHS funded outreach program that would encourage the development of a practical, effective and interdisciplinary model that would best utilize the strengths of the various professions involved. The model developed should be one that is adaptable to a variety of environments and health care settings across the country.

Question 5. You wondered in your statement how many elderly people have been sentenced to a life of institutionalized chemical restraint because they manifested adverse drug reactions which were misdiagnosed as mental illness or diseases of old age. Is there any kind of empirical data on that question? I believe such information would not only help prevent that kind of situation, assuming they exist, but could well save lives through some sort of intervention. If such information isn't available, do you have any suggestions as to how we could obtain it?

Response: We can only speculate how often this occurs. It is certainly not common but I am confident that this scenario does indeed occur. Many medications have adverse effects on the central nervous system of elderly patients including the heart drugs digoxin and Inderal, the ulcer medication Tagamet, most sleeping medications, antidepressant drugs and many others. I have seen examples of how this scenario can develop. One 85 year old patient that I once saw was admitted to the hospital after developing severe behavioral problems at home. She was treated with psychotropic medications for three weeks to control her behavior and it was obvious that in her condition she would not have been able to take care of herself at home. Just before she was to be transferred to a nursing home it was discovered that her behavioral problems were caused by the corticosteroid eye drops that she had been using prior to her admission to the hospital. Had this not been discovered the patient would have been unwillingly transferred to the nursing home, would most likely have been given more sedatives and tranquilizers to control her, and would probably have remained in that unfortunate situation for the remainder of her life.

I don't present this scenario to be melodramatic for I have seen enough patients like the one above to know that it does occur but one can only guess how often. I certainly don't think that in occurs in thousands of patients, however I do feel that it does occur more frequently than we would like to admit.

The example that I provided above, and the many varieties of this scenario can often be prevented by constant vigilance, especially of patients who are at high risk of experiencing adverse drug reactions, such as the frail elderly who are consuming many and/or high risk medications. The most effective way of preventing this problem is to constantly attempt to determine whether a patient's change in condition or new symptoms are the result of medications.

Question 6. How serious is the problem of poor patient compliance, especially as it pertains to the use of non-prescription, over-the-counter medications taken while an individual was also taking prescribed medication?

Response: What this question refers to is not poor compliance, but rather drug-drug interaction between prescription and non-prescription, over-the-counter (OTC) medications. This type of interaction is common. It is well known that many commonly used OTC medications can interact with prescription medications. For example, aspirin can interact with the blood thinner Coumadin to cause bleeding, antacids may prevent the proper absorption of many medications and certain cold and allergy medications may interact with the class of antidepressants known as MAO inhibitors to cause a dangerous rise in blood pressure possibly resulting in stroke. The problem of prescription-OTC drug interactions can best be prevented by encouraging consumers to talk to their pharmacist or physician about taking non-prescription medications concurrently with their prescription medications.

I would like to add that we can expect this problem to occur more frequently as the result of the current push to change many medications from prescription to OTC status.

Question 7. In your testimony, you briefly referred to an ongoing study of medication misuse in nursing homes. What have been your findings to date in this study?

Response: The studies that I referred to are those that have looked at medication consumption patterns in elderly nursing home patients and the factors that have favorably influenced those patterns. A number of studies have shown that the rational use of medications can be promoted, most commonly through interdisciplinary programs that routinely review patient's drug therapy. Studies have shown that physicians, nurses, pharmacists and other health professionals can work effectively as a team by frequently evaluating and re-evaluating the patient's condition and need for medication. What results from this constant vigilance is a pattern of medication use that maximizes the therapeutic potential of medications while minimizing the potential for adverse drug reactions, drug interactions and related problems.

I would like to add that in my experience physicians are generally quite receptive to the suggestions of pharmacists regarding alterations in drug therapy. In the class that I teach on Nursing Home Pharmacy Practice I have observed that almost half of the drug therapy suggestions provide to physicians by pharmacy students are accepted. These observations and others conclude that the key to successful medication management in the nursing home patient is the interdisciplinary review of the entire patient.

Question 8 Why is there not more testing of drugs in the elderly prior to marketing?

Response: Some pharmaceutical firms voluntarily perform geriatric research studies prior to marketing a drug. This research may be designed to develop geriatric dosage guidelines or to learn how a particular medication is eliminated from the body. While this type of research is occasionally performed it is true that this is usually not the case.

There are many reasons why this testing is not performed more frequently. First, this type of testing takes additional time. This delays the marketing of the drug product being tested thereby shortening its period of patent protection. The testing is also expensive since testing in the elderly is often quite involved. Because of the complexities of geriatric studies this testing is often more expensive than traditional clinical studies using younger patients. This type of testing is also difficult to conduct and interpret since most elderly patients are already receiving other medications and have a number of concurrent diagnoses.

I hope that these responses adequately address the questions posed by you and your colleagues. If you would like further clarification or comment please feel free to contact me. I would like to express my thanks to you and your committee for holding this important hearing.

Sincerely,

William Simonson, Pharm.D.
Associate Professor

APPENDIX 3

CORRESPONDENCE AND ADDITIONAL SUBMITTED TESTIMONY

Written Testimony prepared for hearings, 20 July 1987, by the Senate Special Committee on Aging, Senator John Mecher (D-Mont), Chairman

DRUG USE AND THE ELDERLY

Item 1

Some Observations and Recommendations

by

Peter P. Lamy, PhD

Dr. Lamy is Professor and Director, The Center for the Study of Pharmacy and Therapeutics for the Elderly; Director, The Parke Davis Center for the Education of the Elderly; Chairman, Department of Pharmacy Practice and Administrative Science, School of Pharmacy and Research Professor, Epidemiology and Preventive Medicine, School of Medicine, University of Maryland at Baltimore, Baltimore, MD 21201. Dr. Lamy is a Fellow, American Geriatrics Society; a Fellow, The Gerontological Society of America; a Fellow, The American College of Clinical Pharmacology; a Fellow, American Association for the Advancement of Science; and a member, American Society of Clinical Pharmacology and Therapeutics.

DRUG USE AND THE ELDERLY

1.0 BACKGROUND INFORMATION

- 1.1 The Elderly
- 1.2 The Health Status of the Elderly
- 1.3 Where are the Elderly?

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- 2.2 Variability of Drug Use
- 2.3 Possible Future Changes
- 2.4 Prescription Drugs: Still Cost-Effective

3.0 ONE OUTCOME OF MULTIPLE DRUG USE: ADRs

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- 3.3 Possible Reasons for Adverse Drug Reactions

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- 4.2 Focus on Home Care: The Nursing Home Without Walls
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- 4.5 Funding and Oversight

1.0. BACKGROUND INFORMATION

1.1 The Elderly:

There are approximately 22 million persons between the ages of 55 and 64 years and 27 million 65 years old and over. Those 49 million people account for 21% of the American population. Those 60 and over account for 17%, and those 65 and over account for 12%. It is important to realize that the aging population itself is aging, those 85 years old and over constituting the fastest-growing segment of the US population.

1.2 The Health Status of the Elderly:

At least 80% of those 65 years old and over suffer from one chronic disease and of those, as many as 40% may suffer from two or more chronic diseases. In once recent study (Anderson RJ, Excerpta Medica 5:26, 1982) of 102 elderly hypertensive patients, it has been shown that almost 40% also suffered from degenerative joint disease (osteoarthritis), some 25 to 30% suffered from diabetes mellitus, 20% from congestive heart failure, angina, or cerebrovascular disease. Thus, multiple pathology in about 30 to 40% of the elderly is the rule, rather than the exception. Most often, elderly suffer from hypertension. As many as 40 to 60% of elderly are thought to suffer from this problem, which is a risk factor for cardiovascular, cardiac and cerebrovascular problems and ought to be treated. Hypertension occurs more often in females than in males. The health, social and economic problems of the elderly, particularly those 70 years old and over, are those of females. Females, among the very old outnumber males by a ratio of 3:1.

Those over 65 represented 25% of all physician visits in the US in 1986. Almost 162 million visits were by females and 105 million by males, the rest being unspecified.

The aging of the population 65 years old and over has many implications. For example, among those 65 to 74 years old who may be hospitalized, only 4% are referred to long term care upon discharge from the acute care hospital. However, among those 85 years old and over, almost 25% are referred to long term care.

The aging of the older population has other implications to health care. Chronic disabilities occur in 15% of the total US population, but in 66% of those 85 years old and older.

1.3 Where are the Elderly?

Only about 5% of the elderly, or 1.4 million, are cared for in nursing homes. However, for every elderly nursing home resident there are already four adults living in the community of similar age afflicated with equally serious medical problems. Most at risk are those livng alone. In 1987, 8.8 million elderly live alone (those living alone make more medication errors). Sixty-seven percent of those are elderly widows and 14% other elderly females. Thus, females account for 81% of those living alone.

Elderly living in the community may be divided into one of four major categories:

1. Independent
2. Independence threatened
3. Independence delegated
4. Dependent

An elderly woman with osteoarthritis and/or asymptomatic coronary artery disease may be medically stable. However, she may lose "independent" status when coronary artery disease progresses or if osteoarthritis gets worse. She may then be unable to pursue activities of daily living, such as shopping, threatening her independence. Worsening of a disease process may occur more rapidly when medications which are needed are not available.

When independence is delegated, family caregivers often become responsible for the community-living patient. On the average, the caregiver's age is slightly more than 60 years of age and many, indeed, are as old as the patient being cared for. Often, "caregiving" involves 124 hrs/week. Caregivers, therefore, are often exhausted and depressed, needing themselves multiple medications.

2.0 DRUG USE FOR AND BY THE ELDERLY

2.1 An Overview:

Only prescription drugs will be discussed, although 40% of all drugs used in nursing homes are non-prescription drugs and 66% of community-living elderly use non-prescription products.

The data base is poor. Often, data are based on manufacturers' sales, or sales by wholesalers, or on prescriptions dispensed. Actual use data are scarce.

It is known that elderly often lack financial resources needed to purchase prescription drugs. Some studies have indicated that as many as 36% of the elderly may, at times, have problems purchasing their drugs.

It is also known that 40% of elderly patients will stop taking a chronic care drug within the first year of its use. Nevertheless, is it generally agreed that the elderly (12% of the population) receive about 32% of all prescription drugs, and that 70% of all drugs prescribed for the elderly are chronic care drugs. In 1986, new drug therapy accounted for almost 91 million prescriptions for those over 65, but there were 254 million refill prescriptions (in contrast, new prescriptions outranked refill prescriptions for those under 65). Yet, questions remain.

In one study (Br Med J 294:289, 1987), underreporting of medications was common and increased as the number of prescribed drugs increased. In general, it is felt that there is still a significant incidence of inappropriate prescribing for the elderly (JR Coll Phys 21:39, 1987). It is generally believed that community-living elderly use about three prescription drugs/day and possibly two non-prescription drugs.

2.2 Variability of Drug Use:

Drug use varies significantly with the site of care and with the age of the patient. Drug use is probably highest in nursing homes. About 45% of patients over 65 in US nursing homes are on five of more prescription drugs a day (Table I):

TABLE I

PRESCRIPTION DRUG USE

	Age/Location of Patient		
No of Rx Products	65+/NH (%)	65+ non-NH (%)	65- (%)
One	12.0	27.4	43.9
Two	14.0	21.5	25.1
Three	14.8	16.2	13.3
Four	14.3	11.6	7.3
Five or more	44.9	23.4	10.4

Six of the ten most often prescribed drugs for the older-old are cardiovascular drugs (antihypartensives, digoxin, potassium supplements). Beta-blockers represent 17.6% of cardiovascular drug use for community-living elderly (over 35% for those less than 65 years of age) but only 4.4% for nursing home residents.

Major tranquilizers represent 12.5% of all psychotropic drugs used for community-living elderly, but they account for almost 61% of all psychotropics used for nursing home residents (Table II):

TABLE II

SPECIFIC DRUG CATEGORIES

Drug Category	65+/NH (%)	65+/ non-NH (%)	65-(%)
Cardiovascular			
Beta-blockers	4.4	17.8	35.2
Ca antagonists	2.9	8.6	8.6
Vasodilators	29.5	26.5	16.2
Digitalis	29.2	12.5	5.4
Psychotropics			
Antipsychotics	60.5	12.5	14.8
Anti-anxiety agents	17.1	59.0	51.0
Antidepressants	12.3	16.0	18.1

The prevalence of antipsychotic drug use apparently varies widely among nursing homes, usage increasing with nursing home size and being inversely related to the ratio of nursing home staff to patient.

The use of psychotropic drugs for nursing home residents is also mirrored in a listing of the top 8 drugs used (Table III):

TABLE III

THE MOST OFTEN PRESCRIBED DRUGS

Rank	Over 65/NH	Over 65/non-NH	Under 65
1	Digoxin	HCTZ/triamterene	Codeine/APAP
2	Furosemide	Digoxin	Amoxicillin
3	Potassium Cl	Potassium Cl	Norethin/ethinyl
4	Dipyridamole	Nitroglycerin	HCTZ/triamterene
5	Nitroglycerin	Furosemide	Penicillin V Pot
6	Haloperidol	Dipyridamole	Ibuprofen
7	Thioridazine	Propranolol	Theophylline
8	HCTZ/triamterene	Codeine/APAP	Estrogens

The two antipsychotics (haloperidol and thioridazine) which rank high in use for nursing home residents rank only 99th and 90th for community-living elderly.

Six of the top 12 diagnoses and the top 12 drug groups for patients over 65 in 1986 were cardiovascular, with the top 12 representing 54% of all diagnoses and 64% of all drug therapy (the two drug categories whose use increases with increasing age are the cardiovascular drugs and the nonsteroidal anti-inflammatory drugs).

2.3 Possible Future Changes:

Major changes (and concomitant cost increases?) are anticipated in the field of hypertension management. For example, a committee of the American Society of Hypertension (ASH), chaired by Dr. Norman Kaplan, reported at the 1987 meeting in New York that selection of a diuretic in the step-care approach to the management of hypertension seems increasingly inappropriate and outdated. For most patients, treatment should begin with a single agent, selected empirically or on the basis of age, race, coincident conditions such as hyperglycemia or hyperlipidemia, or by renin profiling.

Among antihypertensive drugs, the use of ACE inhibitors and calcium antagonists is rising fast (in the overall market). For example, first-quarter (1987) sales for calcium antagonists were $146 million, up 24% from the same period in 1986.

2.4. Prescription Drugs: Still Cost Effective:

In general, prescription drugs are still relatively inexpensive compared to more labor or technology intensive modalities of health care. They are and remain the front line of medical care for the elderly and are probably most cost effective. For example, the use of cimetidine to control duodenal ulcers resulted in an estimated 26 to 70% saving for Medicaid in Michigan in its first year of use by reducing the need for surgery. Similarly, it has been estimated that lithium treatment of manic-depressive illness has saved $ 4 billion during the last decade.

Enrollment in a pharmaceutical assistance program in New Jersey, following the establishment of that program, was associated with a reduction in expenditures for hospital-based procedures. This latter point is of extreme importance. Of the 27 million elderly, approximately 25% can probably expect to be stricken with cancer. Antineoplastic agents are covered only when patients are cared for in a hospice or are hospitalized. The daily hospital rate is probably $ 250/day. A vial of one antineoplastic (chemotherapeutic) agent may be $ 90 and the patient may need two to three vials of just this one agent. This does not take into consideration pre-treatment activities, such as hydration, for example. Thus, patients are often hospitalized in an effort to protect them from high drug expenditures. Yet, these drugs could be administered in the home at considerable savings to the system.

3.0 ONE OUTCOME OF MULTIPLE DRUGS USE: ADVERSE DRUG REACTIONS

3.1 Prevalence of Adverse Drug Reactions

There is no agreement as to the frequency of adverse drug reactions. One study (N Engl J Med 304:638 1981) showed that 36% of patients on a general medical service had an iatrogenic illness, often due to drugs. Another (N Engl J Med 291:824, 1974) showed that there undesirable reactions occur most often in patients receiving multiple drugs. Deaths attributed to drugs occurred at a rate of 2.4 per 1000 patients (J Allergy Clin Immunol 74:555, 1984). The FDA expects reports to increase sharply (in 1986: 57,000 reports, a ten-fold increase over the last 5 years, going to over 100,000 in a few years). Most involve well-known drugs. One-third of all ADR hospitalization reports involved elderly, as did over 50% of all death reports. Thus, elderly are more susceptible to adverse drug reactions and to their effects.

Drug interactions occur more often in elderly than in younger patients. They occur most often in long-term care institutions and in patients with multiple pathology receiving multiple drugs.

3.2 Some Results of Adverse Drug Reactions:

One example of a potential problem of geriatric drug therapy, in the presence of multiple pathology and concurrent drugs, will be used to highlight the risk to which elderly patients may be exposed. Drugs used to treat several diseases and problems can cause dementia. Many drugs that block the effect of acetylcholine, either as a primary (desired) effect or as an undesired (adverse reaction) effect, are used in the treatment of Parkinson's disease, insomnia, hypertension, colds, depression, and psychoses. Drug-induced dementia is even more common as a cause of reversible dementia than is depression. Indeed, drugs are the most common cause of a syndrome that has been labeled "pseudo-dementia".

Side effects of medications, especially "minor" symptoms, reduce the cost-effectiveness of chronic disease management to a considerable degree. Therefore, diminishing negative side effects of medications and improving the patient's and caregiver's quality-of-life satisfaction are and must be essential goals of chronic disease management. This demands an intimate knowledge of a drug's action, which is perhaps lacking at times.

While quality-of-life has been an important parameter of clinical decision-making for severe diseases (cancer, renal failure) for some time, it has now been recognized that, given the high prevalence of chronic disabilities among the older population, patient adherence to an agreed-upon regimen, linked to quality-of-life perceptions, must have a high health policy priority.

The need for this priority is still not universally recognized. For example, in the general population, in 1984, there were more than 125,000 deaths and several hundred thousand hospitalizations due to noncompliance with cardiovascular drugs alone (six of thee 10 most frequently used drugs for patients 75 years old and over are cardiovascular drugs). In addition, approximately 20 million work days were lost representing an overall cost of $1.5 billion to the national economy simply because prescribed cardiovascular drugs were not taken properly. HHS Associate Secretary Robert Windom and FDA Commissioner Frank Young have termed this "the other drug problem". They have stated that up to one-half of the 1.6 billion prescriptions each year are taken improperly. Pharmacists' (and other health care specialists') intervention and compliance efforts have proven that this problem can be alleviated to a large degree. Efforts, though, are limited due to lack of reimbursement policies.

3.3 Possible Reasons for Adverse Drug Reactions

A major problem is the lack of a sufficient knowledge base. The problem of insufficient knowledge and education about geriatrics and gerontology is global, affecting both human services and medical fields. While it is accepted that drugs are the most cost-effective modality of chronic disease management (OTA, 1985), very little is known about altered drug action in the elderly, particularly the very old, especially in the presence of multiple pathology and multiple drug use (which is often the rule, rather than the exception).

In part, that lack of knowledge can be explained by the fact that rates of functional decline (aging) vary enormously from person to person and from organ to organ within a single person. To some degree, though, "insufficient knowledge" in fact relates to "insufficient dissemination" of current knowledge and its application to geriatric practice (Table IV) and a continuing "traditional approach" to the elderly patient, which uses chronological age as a basis, rather than "functional", "socio-economic", or "dependency" status (Table V).

Table IV

GE-RELATED CHANGES AND THEIR POSSIBLE EEFFECTS ON ACTION OF ANTIHYPERTENSIVES

rgan/System	Change with Age	Possible Effect
rain	Cerebral blood flow decreased by 25% Cerebral autoregulation impaired.	Use drugs that preserve cerebral blood flow. Caution: hyperfusion (?) stroke (?)
	Increased permeability of blood/brain barrier	Exaggerated CNS effects by lipid-soluble drugs: clonidine, methyldopa, metoprolol, propranolol
ardio- ascular	A poor homeostatic system. Impaired control and vascular reactivity.	
	Deterioration of conducting system.	Caution: drugs that interfere with interfere with cardiac impulse (beta blockers).
	Between ages 20 & 80, a 90% loss of vessel elasticity & distensibility	Greater fall in BP with decreased in blood volume. Increased risk to hypotension, hypovolemia
	Baroreceptor sensitivity decreased.	Altered compensatory mechanism drug induced fall in BP.
	Vascular aging (aortic arch), attenuated beta-adrenergic response, blunted postural reflexes, decreased body water, varicose veins, etc.	Increased risk to drug-induced orthostatic hypotension. Caution with diuretics, ganglionic blockers, vasodilators
enal	By age 80, GFR decreased by 25%. Renal blood flow by 50%. Tubular function decreased by 7% per decade	Ability to adjust sodium balance is decreased. Caution: sodium depleting drugs, reduced dietary intake. Increased danger to diuretic induced water intoxication, hyponatremia. May have to reduce dose of renally excreted drugs. Defective thirst mechanism and impaired renal concentrating ability: higher risk to dehydration.

Table V

NEW APPROACHES TO THE AGED

Old	New
Disease Specific Approach	Care Objectives
	Intervention Options
	Management Plan
Aging, Elderly, Old	Chronically Ill
	Dependency*
	Independent Dependency threatened Dependency delegated Dependent medically economically socially
	Kidney Impaired
	Liver Impaired
	Medically Vulnerable
Individual Responsibility	Shared Responsibility
	Maintaining Reserve Capacity
	Provider-Assisted Self-Care

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*Has also been expressed as follows:

a. Fully capable in necessary areas
b. Capable but frail: could use assistance in areas such as shopping
c. Intermittently incapable: subject to temporary situational crises of moderate acuteness (cannot shop in inclement weather; exacerbations of medical disorders such as arthritis
d. Incapable in important areas: severe impairment of vision; non-ambulatory due to amputation
e. Homebound and dependent, confused, cannot transfer from bed

Finally, insufficient knowledge about drugs must be related to the fact that studies on drug use and drug action in the elderly are largely lacking, having taken a back seat to studies elucidating the reasons for aging and similar topics.

Among other reasons for adverse drug effects and interactions in the elderly are physiological and pathophysiological changes with age, multiple drug use, mismanagement of drugs by both providers and patients (as well as caregivers) and poor supervision. Mismanagement of drugs can be expected to increase in view of the fact that the home care segment is the fastest-growing segment of health care for the elderly. According to the Royal College of Physicians (J R Coll Phys 18:7, 1984), supervision of chronic care medications is poor, accounting for many adverse effects and, according to the US College of Physicians (Ann Intern Med 105:454, 1986), physicians too often do not participate in home care.

4.0 RECOMMENDATIONS FOR CONGRESSIONAL ACTION

4.1 Background Considerations:

Congress is currently involved in discussing reimbursement of drugs for ambulatory elderly under Medicare while, at the same time, considering coverage of catastrophic illness. Congress is also requiring the HHS Secretary to revise Federal rules governing nursing homes, to improve the quality of care and the protection of patient's rights. This action follows a report, in 1986, by the Institute of Medicine, an arm of the National Academy of Science. The report found that patients received "shockingly deficient" care in many nursing homes that receive Federal funds for Medicare and Medicaid patients. The Institute noted that patients in these homes were "likely to have their rights ignored or violated and may even be subject to physical abuse". Congress subsequently perceived correctly that new statutory standards for nursing homes are needed.

One of these rights, although not stated explicitly nor alluded to, is the rational and correct use of drugs in the management of chronic diseases. Perhaps these hearings can serve to facilitate a new statutory approach to this problem in a manner similar to the facilitating effect that the IOM report had.

To achieve this end, it is likely that a multifaceted approach is needed, i.e. the creation of a data base, its evaluation, and the development and dissemination of educational materials based on the continuously updated data base. Finally, and most importantly, there needs to be a continuous quality-of-care review of the therapeutic outcome of drug use.

While the FDA still has not mandated testing of drugs in the elderly after several years of hearings and proposals, one would assume that it will do so soon. That, alone, will not serve to ameliorate the problem. This will address only characteristics of new drugs and most of the problems of drug use revolve around old and well-known drugs. Congress has several options to create a better therapeutic milieu for elderly persons needing medications.

4.2 Focus on Home Care: The Nursing Home Without Walls:

Home care is the fastest-growing sector of health care for the elderly. As previously pointed out, for every elderly nursing home resident, there are already four adults living in the community of equal age with similar medical problems, but more serious problems in socio-economic support. Dr. Butler, some time ago, suggested the creation of the "Teaching Nursing Home". The nursing home population will remain static, not least because there will be a shortage of nursing home beds and nurses. Thus, creation of the concept of the "Teaching Nursing Home Without Walls" must be a major priority. It will correlate well with NIA's call for an interdisciplinary, community based long-term care system.

It is important to point out here that management of drugs is more difficult in this sector than in the more structured nursing home sector. One approach to ameliorate this problem might be funding of "compliance packaging". The United States Pharmacopoeia has approved "Med-Pak". Studies have shown that over 20% of all admissions of elderly to nursing homes are due to the elderly patient's inability to self-administer medications. Medicaid has consistently refused to reimburse for packaging which will, among other benefits, enhance a patient's ability to remain at home by making it easier to self-administer medications. This packaging could also be used to create a data base on actual use of drugs and for drug utilization review.

4.3 Evaluate, Support and Expand the Role of the Pharmacist:

In 1974, the Federal government mandated that pharmacists review, on a monthly basis, the therapeutic regimen of all federally-financed SNF patients. In a Report to Congress, entitled "Problems Remain in Reviews of Medicaid-financed Drug Therapy in Nursing Homes" (June 25, 1980), the Comptroller General found these services effective clinically and economically, but also pointed to the need for an expanded data base. HCFA, in 1987, expanded the role of pharmacists to include ICF patients, but the problem of a knowledge base remains.

In the meantime, requests to the HHS Secretary have pointed to the need for the same function in the home care sector, since many of these patients suffer from problems very similar to those seen in the nursing home sector.

The problem of the knowledge base has been addressed by Pharmacy in several ways. One was the publication by the American Association of Colleges of Pharmacy of the text "Pharmacy Practice for the Geriatric Patient", which is being used by many Schools of Pharmacy for teaching and continuing education purposes. A different approach was used by the University of Maryland School of Pharmacy, which, funded by the

Andrus Foundation, originated and presented a 32 hour training program on geriatric drug use for rural pharmacists. About 200 pharmacists particiapted in the states of Maryland, Virginia, West Virginia, Delaware, and Pennsylvania. The cost was approximately $15.00/pharmacy prectitioner/hour. It is of note that the NIA has not supported any Pharmacy efforts so far, though the AoA has. It is noteworthy that the State of Pennsylvania has addressed the School of Pharmacy with a request to offer this progrm on a wider basis in that state.

But Pharmacy's role in achieving rational and correct use in long term care is greater than that suggested by its service role. At a recent meeting on geriatric pharmacology in Baltimore, co-sponsored by the NIA, it was reported that much of the teaching functions in geriatric clinical pharmacology programs was performed by pharmacists. Yet, the NIA has to this point not supported any training programs for pharmacists similar in scope and nature to those developed for physicians and dentists. Indeed,, it has never appointed a pharmacist to its National Advisory Council. The NIA should be directed to address these issues urgently, while HCFA should be directed to study the need for therapeutic regimen review in the home care sector.

4.4 Creation of a Continuously Updated Data Base:

Congress should encourage and require increased post-marketing surveillance of drug use. Federal funds are supporting Medicaid patients to a considerable degree and Congress should require that the data base available through Medicaid funding of prescription drug use be made available to qualified pharmacoepidemiologists. To a degree, individuals have already used these data, but only to a small degree. One outcome, for example, although it did not and could not show cause and effect, is the realization that certain beta blockers probably cause more CNS problems in the elderly than otners.

While the Medicaid data base is probably the most promising and the largest, other likely data bases should not be overlooked. For example, data bases created by large nursing home chains might be available, as may be those from large mail-order prescription operations. Furthermore, it has been estimated that, in a relatively short time, almost 50% of the US population will receive health care from a "managed care" system, whicn is likely to have access to a large, specific data base (Puget Sound, for example).

4.4.1 An Example How This Data Base Could be Created:

Using the School of Pharmacy, University of Maryland, as an example, one could suggest the following sequence:

Drug Policy Center: Recently established at the School of Pharmacy, its Associate Director, Dr. Palumbo, has completed the second of two major federally-financed studies on drug use in nursing homes. The Center is a joint effort of the School of Pharmacy and the UMBC Policy Sciences graduate program. This unique combination places the Center in an ideal position to respond to and evaluate problems such as those being addressed. The Center could be charged (with appropriate funding) to collect Medicaid and other data on drug use in the long-term care sector and analyze these data. The data base would then be evaluated in conjunction with **The Center for the Study of Pharmacy and Therapeutics for the Elderly:** Established some eight years ago, the Center has as its primary function the facilitation of gerontological research (Pharmacology, Pharmaceutics). A second, and major, function of the Center is the development of educational programs. It discharges that responsibility in several ways. One is the collection and dissemination of appropriate information through its ElderCare Newsletter, which now reaches approximately 29,000 health care professionals (see attachment). Through its Parke Davis Center for the Education of the Elderly, it has developed and continues to do so, pamphlets directed to the consumer, which aim to educate the consumer on various aspects of drug use, nutrition, as well as preventive care. The Parke Davis Center has also developed two major audiovisual tapes, describing drug use for the elderly and the elderly's concerns, both of which have been shown on national television in some 40 states. Finally, through its Elder Health Program, which has received an Award of Merit from the HHS Secretary, it addresses consumers directly. This program has been replicated in many states.

The Center also addresses educational needs of professionals by originating and presenting continuing education programs on a local, state, national, and international level. Furthermore, the Center supports several residencies and fellowships (in long-term care, home care, and drug dosage development for the elderly).

The Center would refer back to the Drug Policy Center appropriate information for formulation of policy recommendations.

4.5 Funding and Oversight:

It is proposed that efforts such as those outlined about be funded and supervised by the National Institute on Aging. While it is realized that this may not necessarily conform to the charge the NIA originally received, these efforts are of sufficient importance to be addressed by the premier organization in aging.

It is further strongly suggested that the NIA appoint an oversight committee different from its current National Advisory Council. It is suggested that the NIA is deficient in its approach to drug use (perhaps because there is not a pharmacist either on its staff or on its committee). Pharmacy-educated and prepared practitioners, long charged by the Federal government with review of nursing home patients' medication regimen, would likely add a much different dimension to these efforts.

This recommendation, if enacted, is in concordance with the NIA call for an interdisciplinary, community-based long-term care system. It would then have the means to help originate and coordinate such a system.

Item 2

SENATE AGING COMMITTEE TESTIMONY

TESTIMONY OF DR J DAVID MCCAY, IN PRIVATE CONSULTANT PHARMACY PRACTICE ·
LITTLE ROCK, ARKANSAS
BEFORE SENATOR JOHN MELCHER
CHAIRMAN, SENATE SELECT COMMITTEE ON AGING

FOR MARCH 25, 1988 HEARING
ADVERSE DRUG REACTIONS: ARE SAFEGUARDS ADEQUATE FOR THE ELDERLY

TESTIMONY

My name is David Mccay. I graduated from Pharmacy School in 1965 and have practiced pharmacy in Arkansas for most of that time. I am President of Pharmaceutical Buyers, Inc, a company which negotiates contracts for pharmacists serving the nursing home market. I have been consultant pharmacist since 1977 and continue to consult to two nursing homes in Arkansas.

I appreciate the opportunity to give written testimony before this committee because of my long-standing concern about drug use in the elderly. My perspective is certainly not unique but it should prove to be helpful to this committee. For the last 8 years of my retail career a large portion of my clientele were elderly (both ambulatory and confined to nursing homes). This meant that as a retailer, I was charged with efficiently getting drugs and information to this segment of the population while as a consultant I was charged with reviewing the drug regimens of the same people with a view towards "optimizing" their drug use. Optimizing is my term and it describes my perception of my job as a consultant pharmacist which is to work with the physicians and nursing staff to assure that all patients are getting the drugs that they need when they need them. This includes making recommendations when too many drugs are being prescribed or when drug use is inappropriate for any other reason (such as drug interactions or adverse reactions).

As a provider, I was asked to fill as many as 30 prescriptions for some patients in some months and to absorb the costs when families, third parties or the patients couldn't or wouldn't pay the bill. As a consultant, I have been ignored, cursed and belittled for simply asking physician to consider reducing a patient's drug load. I have also experienced great warmth from some of the lowest paid workers in this industry and I have had the pleasure to work with some physicians whose only concern was the patient's welfare and who actively sought my advice for the purpose of improving the patient's drug regimen.....It is from this perspective that I would like for you to consider the following:

With respect to the topic of this hearing, I am not convinced that safeguards can be designed that will protect our elderly from ill conceived drug regimens as long as physicians are allowed to practice without demonstrating a knowledge of the special needs and concerns of elderly patients. It would be simplistic to say without caveat that the fault lies entirely with physicians. The issue is vastly more complex than that. It would be a mistake, however, not to recognize that a system [as complex as our health delivery system] which allows one segment to operate almost autonomously while all others are subject to various checks and balances is a recipe for disaster.

We must recognize that the problems we are seeing with the elderl relative to drug use is a recent phenomena. There has been an explosion of new drugs, diagnostic techniques and treatment regimens within the last 30 years. There has been a concomitant explosion of the numbers of people in all age groups over 55. These trends will not only continue but are expected to increase over the next 20 to 30 years. In this setting, it should come as no surprise that all healthcare providers have been inundated with information relative to new technology and no one has been asked to absorb more information that the physician. In this age of exponential increases in our information base, the one solution that seems to apply to all disciplines is specialization. The AMA has recognized that no physician can be all things to all patients and has mandated that all physicians be certified in some specialty. What has not been recognized by the AMA is that drug management is just as complex and just as important as other diagnostic and treatment modalities...

IN MY OPINION, NO PROPOSED SOLUTION TO THE DRUG PROBLEM IN THE ELDERLY IS LIKELY TO SUCCEED WHICH DOESN'T RECOGNIZE THE NEED TO SHIFT THE MANAGEMENT OF DRUG REGIMENS ONTO THOSE TRAINED TO DO THE FOLLOWING:

1. EVALUATE ANY SPECIAL NEEDS OF THE POPULATION SEGMENT BEING TREATED.
2. WITH RESPECT TO ANY INDIVIDUAL DRUG, BE ABLE TO WEIGH THE RISKS VERSUS THE BENEFITS TO THE PATIENT.
3. WITH RESPECT TO COMBINATIONS OF DRUGS, BE ABLE TO PREDICT THE LIKELIHOOD OF DRUG-DRUG, DRUG-FOOD, DRUG-DISEASE OR DRUG-LIFESTYLE PROBLEMS.
4. WITH RESPECT TO ALL OF THE ABOVE, BE ABLE TO RECOGNIZE WHEN A PROBLEM IS IATROGENIC [CAUSED BY THE DRUG(S)] RATHER THAN ORGANIC THE OBVIOUS BENEFIT OF WHICH IS PREVENT DRUG RELATED PROBLEMS FROM BEING TREATED WITH OTHER DRUGS.

In my experience, drug problems in the elderly can be classified under the following general headings:

PHYSICIAN GENERATED
1. PRESCRIBING HABITS
2. MISDIAGNOSED DISEASES
3. TIME CONSTRAINTS
4. BEHAVIOR MODIFICATION

PATIENT GENERATED
1. COGNIZANCE
2. FINANCIAL

PHYSICIAN GENERATED

1. PRESCRIBING HABITS. There are some physicians who simply operate by

treating every problem with a drug. I am familiar with some patients in nursing homes with in excess of 30 drug orders. The best information that I can gather is that all complaints are treated with drugs, with very little counseling aimed at helping the patient work through their problems. The patient learns to rely on the Physician and the Pharmacist for the answers to all of their ills.

2. MISDIAGNOSED DISEASES. I am not referring to occasional human error in this instance. I refer to two situations...

A. A tendency to group a variety of illnesses under the diagnosis of SENILE DEMENTIA. Many organic and iatrogenic problems have symptoms which resemble dementias. Many more problems develop when presenting symptoms are considered "just part of the aging process".

B. Iatrogenic disease (for our purpose meaning problems associated with drug use) is a problem of major proportions in the elderly. What we know is that 7% of all hospitalizations of people over 55 are due to drug related disorders. The economic and social costs of this are fairly easy to assess. What we don't know are the costs associated with drug disorders that go unhospitalized. These are real costs which have remained unnoticed by our out-of-site-out-of-mind mentality. Let me describe a generic situation which illustrates my point.

"One advance in diagnosis and testing has pointed out that certain classes of diuretics (drugs used to remove fluid from the body and which are valuable in treating high blood pressure and some heart diseases) can cause a depletion of the body's potassium reserves. Because of the importance of potassium in many body functions, low potassium levels can cause severe, even life threatening problems (high potassium levels can be even more dangerous). Not everyone responds to diuretics in this manner, however, and the only way to know for sure is to periodically draw blood and test for serum potassium levels. It is quite easy to fall into the trap of giving everyone who is taking a diuretic a potassium supplement without benefit of supporting labwork (see note at end of this report).

Patient Jones has developed high blood pressure in the nursing home and Dr Smith starts her on furosemide a potent diuretic. Mrs Jones' blood pressure returns to normal and Dr Smith decides to leave her on Furosemide indefinitely. Because Furosemide is known to deplete potassium in some patients, Dr Smith adds a potassium supplement to mrs Jones drug regimen. Now as is often the case, potassium has a major side effect of gastrointestinal irritation and within 40 days mrs Jones is complaining of stomach pain and the nurses are reporting blood in her stools. Dr Jones knows that potassium can cause GI irritation but because of the time lapse since he started the potassium, he does not mentally connect Mrs Jones' symptoms with the potassium use and decides instead that she has developed an ulcer. To treat the ulcer, he prescribes Tagamet to cut down on acid production, an Antacid to neutralize any residual acid and Valium to treat what he considers the psycogenic origins of the "ulcer". Because of a peculiar reaction that often occurs when Tagamet and certain other drugs (such as valium) are given together, within two weeks, mrs Jones has become confused, anorexic and disoriented. She wanders into other people's room and has become frightened and combative. She is evaluated as having early Alzheimers, is started on an antipsychotic drug and restrained in a geri-chair............"

It is important to note that although this is a dramatization, it represents an amalgam of problems that I and many other consultant pharmacists have noted during the course of our reviews. I can only guess at the cost of this type of situation in terms of dollars and diminished quality of life. My feeling is that the cost would appall even the most hardened observer.

3. TIME CONSTRAINTS. Many physicians have built practices and acquired lifestyles based on large patient loads. For most of the older physicians, they had little choice in this as the demand for medical care outstripped their ability to provide it. What I have seen develop in the nursing home industry is a fairly common system where a physician leaves permanent orders for drugs to meet every anticipated need of the patient. In this way, he avoids many calls from nurses asking for orders to treat various complaints.

4.BEHAVIOR MODIFICATION I believe that this is largely a nursing home phenomena whereby agitated, loud, or disoriented patients are given sedative doses of tranquilizers to render them more manageable for the nursing staff. This is a problem of degrees. In many instances patients are simply too agitated or combative to function in close proximity to other patients. The line between "chemical restraint" and altering behavior patterns for the patient's safety and the safety of those around him is imprecise at best. It is important that the members of this committee know that chemical restraint exists and that solutions need to be sought for the good of the patients and the industry.

PATIENT GENERATED

1.COGNIZANCE. One of my goals in making this report is to make this committee aware of the difficulty in keeping up with the advances in the medical profession. With respect to drugs, even pharmacists have a hard time keeping up with all of the new information on drug actions, reactions and interactions. It is no surprise then that patients would be operating in a void where medicines are concerned. Even with the best efforts of Physicians and Pharmacists to educate patients on the use and abuse of their drugs, all too often patients do abuse their drugs (by abuse, I mean misuse which can be overuse, underuse or inappropriate use). What is disturbing is that as patients get older, their use of prescription drugs increases and with the increase in drug use comes an increase in the opportunity for abuse. In the elderly, it tends to manifest itself in the following manners:

1. Underuse- Patients either forget to take their medications as prescribed or avoid taking them because of financial problems or unpleasant side effects.
2. Overuse-this can range from addiction or habituation to laxatives or controlled substances to the old "if one is good, two is better" problem.
3. Inappropriate use-This can manifest in many ways also such as mixing a prescription drug with other prescription drugs or non-prescription drugs or foods without first consulting a Physician or Pharmacist resulting in harmful interactions. It includes using drugs for problems for which they are not intended, taking other people's drugs and taking out of date drugs.

2.FINANCIAL. This is a fairly straightforward problem where a person is at risk because of his inability to pay for prescription drugs needed to maintain health. In my opinion, the need here is to determine the extent of this problem and its costs both to the taxpayers and to the people affected. The costs are likely to be ones that could be avoided if the medicines were taken correctly such as hospital and nursing home stays and office visits for problems exacerbated by inappropriate drug use.

IN CONCLUSION, IT IS CERTAINLY NOT MY INTENTION TO POINT FINGERS AND ATTACH BLAME FOR THE PROBLEMS I HAVE DESCRIBED. MY MOTIVE IS TO BRING THESE PROBLEMS TO LIGHT AND TO THE EXTENT THAT I AM CAPABLE BE A PART OF THE SOLUTION. AS WITH MOST OF THE PROBLEMS WE FACE TODAY, I BELIEVE THE ANSWER IS IN EDUCATION. OUR JOB AS PROFESSIONALS AND YOUR JOB AS LAW MAKERS IS TO FIRST IDENTIFY THE PROBLEMS AND THEN CHART A COURSE TO THEIR SOLUTIONS WHICH MAKES BEST USE OF THE AVAILABLE TALENT AT OUR DISPOSAL. FOR THE PROBLEMS ASSOCIATED WITH DRUG USE IN THE ELDERLY, I WOULD SUGGEST THAT AT LEAST PART OF THE SOLUTION WOULD BE TO IMMEDIATELY INVOLVE PHARMACISTS TO A GREATER EXTENT IN THE MANAGEMENT OF DRUG REGIMENS. WHERE THIS HAS BEEN DONE, IT HAS PROVEN EFFECTIVE IN REDUCING COSTS AND OPTIMIZING PATIENT'S HEALTH. WHERE WE CAN, WE NEED TO FIRST EDUCATE ALL MEMBERS OF THE MEDICAL PROFESSION ABOUT THE SPECIAL NEEDS OF

THE ELDERLY POPULATION. ALMOST AS IMPORTANT, IN MY OPINION, IS THE NEED TO EDUCATE THE PEOPLE TO WHOM WE MINISTER. I SEE NO SOLUTIONS THAT DO NOT INVOLVE RELINQUISHING SOME TURF ON THE PART OF SOME DISCIPLINES FOR THE GOOD OF THE PATIENT. ON THE OTHER HAND, I SEE NO PROBLEMS THAT CANNOT BE SOLVED BY A WELL INFORMED MEDICAL COMMUNITY AND A WELL INFORMED CONGRESS WILLING TO TAKE THE NECESSARY STEPS TO ALTER THE INERTIA THAT HAS TAKEN US TO THIS POINT OF INQUIRY. THE INERTIA THAT HAS BROUGHT OUR SYSTEM OF MEDICAL CARE THIS FAR IS MUCH LIKE THE ROCKET WE AIMED AT THE MOON. ONCE THE ROCKET LEFT EARTH'S GRAVITY, THERE NEVER WAS A DOUBT ABOUT THE ROCKET'S ABILITY TO GO AS FAR AS THE MOON, IN FACT, IT WAS CAPABLE OF GOING MANY BILLIONS OF MILES FURTHER THAN THE MOON. THE ONLY DOUBT WAS IN OUR ABILITY TO MAKE THE SMALL ADJUSTMENTS IN FLIGHT TRAJECTORY THAT WOULD PUT IT PRECISELY WHERE IT NEEDED TO BE IN ORDER TO BE CAUGHT BY THE MOON'S GRAVITY AND ACHIEVE A STABLE ORBIT. IN MY OPINION, WE KNOW MOST OF WHAT WE NEED TO KNOW IN ORDER TO ASSURE OUR ELDERLY OF OPTIMUM DRUG REGIMENS. THE KEY WILL LIE IN OUR ABILITY TO FINE TUNE THE TRAJECTORY OF OUR EFFORTS SO THAT WE CAN ASSURE ALL OF OUR CITIZENS THAT THE ADVANCES IN MEDICAL CARE ARE NOT OFFSET BY INAPPROPRIATE DRUG USE.

J David McCay, PD

==

Note- WITH THE COOPERATION OF THE ATTENDING PHYSICIAN AT A NURSING HOME TO WHICH I CONSULT, I INSTITUTED A STUDY WHEREBY WE IDENTIFIED ALL OF THE PATIENTS WHO WERE TAKING A POTASSIUM SUPPLEMENT. WE THEN STOPPED THE POTASSIUM ON ALL PATIENTS EXCEPT THOSE WITH CONGESTIVE HEART FAILURE. THE DESIGN OF THE STUDY CALLED FOR TESTING OF POTASSIUM LEVELS ON EACH OF THESE PATIENTS EVERY TWO MONTHS FOR THE FIRST SIX MONTHS THEN EVERY SIX MONTHS THEREAFTER. ANY PATIENT WHOSE POTASSIUM LEVEL FELL BELOW A PREDETERMINED LEVEL WAS TO HAVE THEIR POTASSIUM SUPPLEMEN REINSTITUTED. I SHOULD POINT OUT HERE THAT THIS WAS NOT A SCIENTIFIC STUDY, BUT WAS DONE TO HELP THE MEDICAL AND NURSI STAFF ARRIVE AT A REASONABLE CRITERIA FOR DEALING WITH THE DIURETIC/POTASSIUM PROBLEM. THIS STUDY HAS BEEN ONGOING FOR THE LAST SIX MONTHS AND TO THIS DATE, NO PATIENT HAS HAD TO BE REINSTATED ON POTASSIUM DUE TO A LOW SERUM LEVEL.

JDM

Item 3

APhA
American Pharmaceutical Association
2215 Constitution Avenue, NW
Washington, DC 20037
(202) 628-4410 FAX (202) 783-2351
The National Professional Society of Pharmacists
John F Schlegel, PharmD
President and CEO
Charles R. Green
Chairman of the Board

April 8, 1988

The Honorable John Melcher
Chairman, Senate Special Committee
on Aging
Room G41
Dirksen Senate Office Building
Washington, DC 20510-6400

Dear Senator Melcher:

The American Pharmaceutical Association (APhA) is pleased to submit comments for your March 25, 1988 hearing record on "Adverse Drug Reactions: Are Safeguards Adequate for the Elderly?" APhA is the national professional society of pharmacists representing the third largest health profession, comprising more than 150,000 pharmacy practitioners, pharmaceutical scientists and pharmacy students.

APhA shares the concerns you expressed in your opening statement at the March 25 hearing about adverse drug reactions affecting the elderly and the failure of current adverse drug reaction reporting systems to collect complete information on ADRs. In addition, APhA is concerned about the number and severity of adverse health outcomes that result from the failure of many patients of all ages to follow instructions for taking medications. Some studies indicate that as a result of failure to take medication as prescribed, 125,000 people die each year, hundreds of thousands are hospitalized, and millions of workdays are lost. APhA thus agrees that both the government and the health care community must begin to more thoroughly address and resolve these concerns.

The remainder of this letter will address three basic issues. First, I will discuss the need for a more effective postmarketing surveillance system and the role pharmacists currently play in preventing adverse drug reactions and interactions. Second, I will discuss the role of the pharmacist in ensuring rational drug therapy. Third, I will discuss the need for appropriate financial incentives for all health care professionals to ensure that they aggressively participate in postmarketing surveillance systems and drug therapy quality assurance programs.

APhA has long been concerned with the problems associated with adverse drug reactions and the need to have a better postmarketing surveillance system for both identifying ADRs and collecting information on ADRs. The APhA House of Delegates first adopted policy on the issue of an ADR reporting system in 1967 and has adopted policies related to this issue on numerous occasions since then. APhA thus recognizes the need for a better reporting and monitoring system to ensure that the most up-to-date information on prescription drug products is available to all health care professionals. The more information that is available on potential adverse drug reactions, the more likely it will be that they can be avoided through appropriate prescribing, counseling and monitoring. APhA believes that pharmacists, as the most readily accessible health care professionals, are in an excellent position to obtain information about patients' adverse reactions to prescription medications and to report that information to FDA.

The role of the pharmacist in preventing both ADRs and serious drug interactions cannot be overstated. Pharmacists, who have extensive education and training, are experts in ensuring the rational use of drugs and in communicating that information to patients and other health care professionals. APhA strongly believes that all patients receiving medication are entitled to comprehensive pharmaceutical services, which only pharmacists can provide. These essential services, which include maintaining patients' medication profiles and counseling patients, are even more critical when providing care to the nation's elderly. Studies at the University of Michigan have shown that 15% of the elderly population takes four or more medications concurrently. The pharmacist's review of all medications taken by a patient plays an important part in avoiding serious adverse drug reactions, as well as serious drug interactions, that may result in hospitalization or death.

In addition to the counseling activities that pharmacists perform in connection with their medication dispensing activities, pharmacists play an active role in quality assurance programs related to drug therapy. These activities also have important implications for preventing adverse drug reactions and serious drug interactions.

One such quality assurance program is Drug Usage Evaluation (DUE). DUE may be defined as a structured, ongoing, organizationally authorized quality assurance process designed to ensure that drugs are used appropriately, safely, and effectively.

Pharmacists, in conducting DUE programs, work with other health care professionals to establish criteria and standards against which to measure drug therapy decisions. Pharmacists then retrospectively review prescription orders in light of diagnosis, lab values, other concurrent prescription orders, and therapeutic outcome to assess quality of care and the economic impact of drug therapy decisions. When less than optimal drug therapy decisions are discovered, the pharmacist intervenes, usually by informing the prescriber about the drug therapy problem and then suggesting alternatives that will lead to a higher quality of care outcome for the patient.

Another type of drug therapy quality assurance activity conducted by pharmacists is the patient-specific drug regimen review. Drug regimen review is a systematic approach to the monitoring of a specific patient's medication regimen to achieve optimal drug therapy for that patient. More specifically, this activity utilizes the valuable and unique body of knowledge that pharmacists possess. This knowledge enables pharmacists to monitor drug regimens for appropriate and necessary drug selection, correct dosages, appropriate follow-up procedures to evaluate therapeutic outcome, and avoidance of excessive side effects, adverse drug reactions, or drug interactions.

Pharmacists in all practice settings can perform this important quality assurance activity. Moreover, pharmacists have received regulatory sanction for this activity in the long term care area. The Health Care Financing Administration (HCFA) requires that pharmacists alone be authorized to conduct drug regimen review activities in both skilled nursing facilities and intermediate care facilities for the mentally retarded.

Finally, APhA believes that if we are to successfully reduce the incidence of adverse drug reactions and drug interactions in the elderly, appropriate incentives must be built into the system to encourage health care providers to more aggressively monitor patients' prescription drug therapy. The service activities we have described in this letter are considered cognitive services for which reimbursement is often not available. APhA believes that unless there are economic incentives for pharmacists, as well as other health care providers, to provide these cognitive services in the absence of products or procedures, the maximum effort from all members of the health care community will not be brought to bear on this problem. APhA would be pleased to work with you and the appropriate regulatory agencies to develop legislative and regulatory responses to address the need to offer health care providers incentives to aggressively attack the problem of adverse drug reactions and drug interactions.

APhA commends the Senate Special Committee on the Aging for its recognition of the serious effects that unmonitored prescription drug therapy can have on the elderly. Recognizing that, even under ideal conditions, the risks of adverse effects of drug therapy can never be reduced to zero, we respectfully urge the Committee to acknowledge and encourage the important role that pharmacists can and do play in ensuring that prescription drug therapy for the elderly is appropriate, rational and as free of risk as current knowledge and practice permit.

Thank you for your consideration of our comments. APhA stands ready to provide any additional information or assistance you may desire.

Sincerely,

John Schlegel

John F. Schlegel, Pharm.D.
President

JFS/ad

Item 4

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO, ILLINOIS 60610 • PHONE (312) 645-5000 • TWX 910-221-0300

JAMES H. SAMMONS, M.D.
Executive Vice President
(645-4300)

March 25, 1988

The Honorable John Melcher
Chairman, Special Committee on Aging
United States Senate
Room SD-G41 Dirksen Senate Office Building
Washington, D.C. 20510

Re: Hearing of March 25 -
Safeguards against Drug
Reactions

Dear Senator Melcher:

The American Medical Association takes this opportunity to submit this letter and the enclosed attachments for the consideration of the Committee and for inclusion in the record of the March 25 hearing on safeguards against adverse drug reactions. The AMA is active in providing physicians with information on the proper use of drugs. One purpose of this information is to avoid, to the degree possible, adverse reactions to the drug therapy selected by the physician.

At the outset, however, it should be kept in mind that drug reactions may result from a number of causes. As a basic proposition, each and every drug is capable of causing a reaction, even when prescribed in accordance with approved labeling for the appropriate medical indication. No drug is assured to be totally safe in its usage. The common aspirin is capable of producing an adverse reaction. Drug reactions may also result from interactions with other drugs, either prescribed appropriately by the same physician, or through more than one physician.

Having addressed briefly potential adverse reactions, which are an infrequent although important aspect of drug therapy, it is equally important that the benefits of drug therapy be kept in mind. Advances in drug development have made possible the ability of the physician to provide treatment not available only a short time ago. The miracles of drug treatment seen every day cannot be over emphasized. Moreover, drug therapy is often the least expensive and most cost-effective component of health care costs.

In prescribing medications, therefore, the physician must weigh the potential benefits of the drug therapy, keeping in mind the possibility of an adverse drug reaction. This professional judgment is made individually on the basis of the condition of each patient.

The situations physicians face in caring for the elderly and the potential in this population for drug interactions must be understood. In a society where people are experiencing a better quality of life for more years than at any time in history, the elderly (who constitute 12% of the population) utilize about 30% of the drugs, prescription and over-the-counter, dispensed in the United States. The elderly commonly have multiple chronic illnesses; therefore, it is not uncommon for an elderly patient to be getting numerous medications in the course of a year for a number of chronic and acute conditions.

The essential element to avoid adverse drug reactions and to assure the best possible care for the elderly is physician education.

Building blocks for providing competent quality health care services for the elderly patient must begin early in a physician's education; therefore, the AMA has encouraged medical schools to focus on the needs of elderly patients. The AMA actively participates and sponsors seminars aimed at improving the ability of practicing physicians in their care of the elderly. For example, in 1985 the AMA was a principal sponsor of an interdisciplinary conference on health policy and quality of care for older Americans and the AMA continues to promote issues relating to care for the elderly.

The American Medical Association is both a major publisher as well as creator of valuable information for physicians on the needs and care of the elderly. Through the Journal of the American Medical Association (JAMA), the AMA publishes important contributions that reach hundreds of thousands of physicians and provide vital information in the ongoing education of physicians that accrues to the benefit of our elderly patients. (An example of this is the attached article, "Assuring the Quality of Health Care for Older Persons," published in JAMA on October 9, 1987.)

Turning to the specific issue that initiated your hearing, adverse drug reactions and the elderly, the AMA and physicians are working to minimize this problem. The AMA has developed a Prescription Abuse Data Synthesis (PADS) model that is used as an important tool in the fight to diminish overprescribing and adverse drug reactions relating to controlled substances. With this reporting tool in place, physicians will have a better idea of how and what drugs their patients may be using as they will be able to identify situations where patients are receiving drugs from multiple sources. PADS works to identify practitioners who misprescibe or overprescribe drugs for their patients, including the elderly. The AMA is pleased to be in the forefront of this activity.

The AMA historically has played a key role in providing physicians and the public with unbiased information on adverse drug reactions and drug interactions. The AMA is both the creator and publisher of AMA Drug Evaluations, a leading work on drug selection and drug information for health professionals. (A copy of the Sixth Edition of AMA Drug Evaluations is attached for your information.)

The AMA also has an active program of public health communications for our patients. Our lead publication, the AMA Family Medical Guide, has sold over 3,400,000 copies. We have just released to bookstores a new publication, also included with this letter, AMA Guide to Prescription and Over-the-Counter Drugs.

The American Medical Association instituted a public information program on drugs with our Patient Medication Information (PMI) leaflets. These tear-off sheets generally are given to the patient. The PMI sheets provide warnings about medications so that adverse reactions can be detected early and appropriate steps taken before harm may be inflicted. The leaflets also attempt to minimize adverse drug interactions by telling the patient: "Before taking this medication, be sure to tell the doctor if you are taking ...." It is estimated that these PMI leaflets encompass approximately 90% of all outpatient medications. (A sample of a PMI leaflet is attached.)

Physicians undertake both an ethical and legal responsibility when they initiate or continue a drug therapy. In the vast majority of patient-physician contacts, these responsibilities are taken seriously and are undertaken in the best interests of the patients.

We are pleased to provide the Committee with this initial statement on the general subject of the hearing. We also will be happy to amplify on the points raised above and to respond to any questions the Committee may have.

Sincerely,

James H. Sammons M.D.

James H. Sammons, M.D.

JHS/bb

cc: Special Committee on Aging
United States Senate

PMI 017 **H-2 Blockers (formerly Cimetidine)**

Patient Medication Instruction Sheet

For: ______________________________

Drug Prescribed: ______________________

Directions for Use: ____________________

____

Special Instructions: ___________________

Please Read This Information Carefully

This sheet tells you about the medicine your doctor has just prescribed for you. If any of this information causes you special concern, check with your doctor. **Keep this and all other medicines out of the reach of children.**

Uses of This Medicine

An H-2 blocker decreases the production of stomach acid; therefore, it is useful in treating and preventing the recurrence of esophageal, stomach and duodenal inflammation and ulcers that are aggravated by acid. H-2 blockers may also be used for other conditions as determined by your doctor.

Before Using This Medicine

BE SURE TO TELL YOUR DOCTOR IF YOU . . .

- are allergic to, or have ever had an unusual reaction to, an H-2 blocker;
- are pregnant or intend to become pregnant while using this medicine;
- are breast-feeding;
- have any medical problems, especially kidney or liver disease;
- are taking any other medicine, especially the following:
  - Anticoagulants (blood thinners)
  - Medicines for anxiety
  - Beta blockers (medicines for the heart and high blood pressure)
  - Medicines for seizures
  - Theophylline (medicine for asthma)

Proper Use of This Medicine

DOSAGE

If you are taking several doses of an H-2 blocker a day, take them with meals and at bedtime for best results, unless otherwise directed by your doctor. If you are taking a single daily dose, it is most often taken at bedtime.

If you miss a dose of this medicine, take it as soon as possible unless it is almost time for your next dose. In this case, do not take the missed dose at all and do not double the next one. Instead, go back to your regular dosing schedule. If you have any questions about this, check with your doctor.

(continued on reverse side)

Antacids may be taken, but not at the same time, with H-2 blockers to help relieve any stomach pain, unless your doctor has told you not to use them. You may want to use antacids at least initially since it may take several days for the H-2 blocker to begin to relieve pain. Space your dose of H-2 blockers and the antacid by at least one, and preferably two, hours.

Remember that certain medicines, such as aspirin, as well as certain foods and drinks, such as alcohol and caffeine-containing beverages, may aggravate your ulcer and make your problem worse. Check with your doctor if your ulcer pain continues or gets worse.

Side Effects of This Medicine

RARE SIDE EFFECTS THAT SHOULD BE REPORTED TO YOUR DOCTOR

- Sore throat and fever
- Unusual bleeding or bruising

POSSIBLE SIGNS OF OVERDOSE THAT SHOULD BE REPORTED TO YOUR DOCTOR

- **Mental confusion (dizziness and mental confusion are more likely to occur in elderly or very ill patients who are usually more sensitive to the effects of an H-2 blocker)**

SIDE EFFECTS THAT MAY OCCUR WITH LARGE DOSES OR LONG-TERM TREATMENT

- Changes in sexual ability
- Swelling of breasts or breast soreness in males

SIDE EFFECTS THAT MAY NOT REQUIRE MEDICAL ATTENTION

These possible side effects may go away during treatment; however, if they persist, contact your doctor.

- Diarrhea
- Dizziness or headache
- Muscle cramps or pain
- Skin rash

Before Discontinuing This Medicine

Take this medicine for the full time of treatment, even if you begin to feel better. Also, be sure to keep your appointments for check-ups so that your doctor will be able to tell you when to stop taking this medicine.

The information in this PMI is selective and does not cover all the possible uses, actions, precautions, side effects, or interactions of this medicine.

This PMI is produced by the AMA, which assumes sole responsibility for its content. Appreciation is acknowledged to the other organizations that provided assistance and information to the AMA and, in particular, the U.S. Pharmacopeia.

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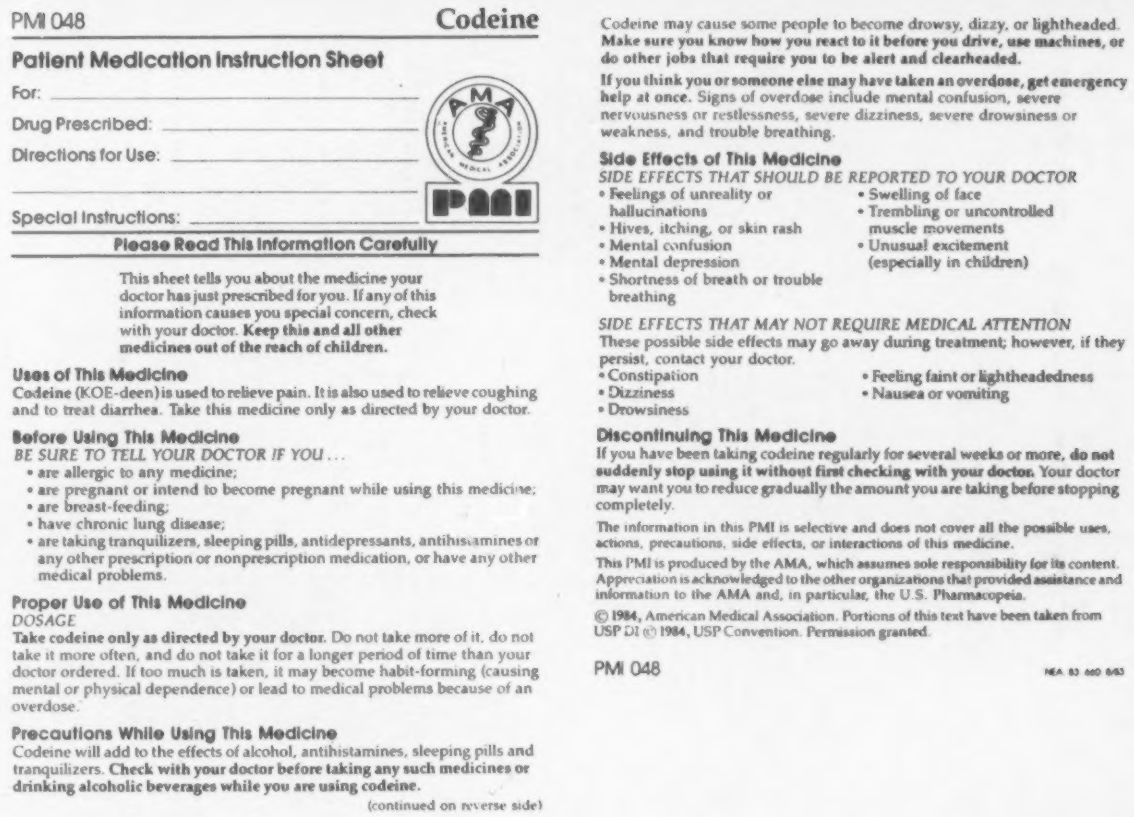

PMI 048 **Codeine**

Patient Medication Instruction Sheet

For: ______________________

Drug Prescribed: ______________________

Directions for Use: ______________________

____

Special Instructions: ______________________

Please Read This Information Carefully

This sheet tells you about the medicine your doctor has just prescribed for you. If any of this information causes you special concern, check with your doctor. **Keep this and all other medicines out of the reach of children.**

Uses of This Medicine

Codeine (KOE-deen) is used to relieve pain. It is also used to relieve coughing and to treat diarrhea. Take this medicine only as directed by your doctor.

Before Using This Medicine

BE SURE TO TELL YOUR DOCTOR IF YOU . . .

- are allergic to any medicine;
- are pregnant or intend to become pregnant while using this medicine;
- are breast-feeding;
- have chronic lung disease;
- are taking tranquilizers, sleeping pills, antidepressants, antihistamines or any other prescription or nonprescription medication, or have any other medical problems.

Proper Use of This Medicine

DOSAGE

Take codeine only as directed by your doctor. Do not take more of it, do not take it more often, and do not take it for a longer period of time than your doctor ordered. If too much is taken, it may become habit-forming (causing mental or physical dependence) or lead to medical problems because of an overdose.

Precautions While Using This Medicine

Codeine will add to the effects of alcohol, antihistamines, sleeping pills and tranquilizers. **Check with your doctor before taking any such medicines or drinking alcoholic beverages while you are using codeine.** Codeine may cause some people to become drowsy, dizzy, or lightheaded. **Make sure you know how you react to it before you drive, use machines, or do other jobs that require you to be alert and clearheaded.**

(continued on reverse side)

If you think you or someone else may have taken an overdose, get emergency help at once. Signs of overdose include mental confusion, severe nervousness or restlessness, severe dizziness, severe drowsiness or weakness, and trouble breathing.

Side Effects of This Medicine

SIDE EFFECTS THAT SHOULD BE REPORTED TO YOUR DOCTOR

- Feelings of unreality or hallucinations
- Hives, itching, or skin rash
- Mental confusion
- Mental depression
- Shortness of breath or trouble breathing
- Swelling of face
- Trembling or uncontrolled muscle movements
- Unusual excitement (especially in children)

SIDE EFFECTS THAT MAY NOT REQUIRE MEDICAL ATTENTION

These possible side effects may go away during treatment; however, if they persist, contact your doctor.

- Constipation
- Dizziness
- Drowsiness
- Feeling faint or lightheadedness
- Nausea or vomiting

Discontinuing This Medicine

If you have been taking codeine regularly for several weeks or more, **do not suddenly stop using it without first checking with your doctor.** Your doctor may want you to reduce gradually the amount you are taking before stopping completely.

The information in this PMI is selective and does not cover all the possible uses, actions, precautions, side effects, or interactions of this medicine.

This PMI is produced by the AMA, which assumes sole responsibility for its content. Appreciation is acknowledged to the other organizations that provided assistance and information to the AMA and, in particular, the U.S. Pharmacopeia.

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PMI 048 MA 83 660 8/83

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Council Report

Elder Abuse and Neglect

Council on Scientific Affairs

Estimates of elder abuse approximate 10% of Americans over 65 years of age; obtaining accurate incidence and prevalence figures is complicated by factors including denial by both the victim and perpetrator and minimization of complaints by health professionals. Broad agreement exists in categorizing elder abuse as physical, psychological, and financial and/or material, despite lack of uniformity in definitions. Systematic scientific investigation provides limited knowledge about the causes of elder abuse. Most experts, however, believe that family problems and conflict are a major precipitating factor. Preliminary hypotheses for elder abuse include dependency, lack of close family ties, family violence, lack of financial resources, psychopathology in the abuser, lack of community support, and certain factors that may precipitate abuse in institutional settings. This report presents potential indicators of physical and psychological abuse, along with classification of elderly individuals at high risk, to assist the health professional in identification and prevention of elder abuse.

(*JAMA* 1987;257:966-971)

RESOLUTION 112 (I-85, adopted) urges the American Medical Association to study and report on diagnostic and treatment guidelines concerning elder abuse and neglect and to develop model legislation for mandatory reporting by physicians of elder abuse.

The AMA has drafted and distributed to state medical associations model state legislation requiring mandatory physician reporting of cases of elder abuse.

Resolution 112 reflects the Association's long-standing commitment to preserve the dignity of the individual, most recently evidenced by its major initiative regarding child abuse and neglect. The resolution asks that *AMA Diagnostic and Treatment Guidelines Concerning Child Abuse and Neglect*, a report of the Council on Scientific Affairs (Report I, 1984 Interim Meeting, adopted), be used as a model in developing the elder abuse guidelines.

Only recently has attention been focused on abuse of the elderly as a major national concern. In a 1981 report, the US House of Representatives Select Committee on Aging called elder abuse "alien to the American ideal." Even the abused elderly were ashamed to admit that their children and others entrusted with their care had mistreated them. For this reason, the report stated, "the abuse of our elderly at the hands of their children until recent times has remained a shameful and hidden problem."[1]

Historical/Sociological Perspective

Abuse and neglect of the elderly in the western world tends to be regarded as a relatively recent phenomenon. However, historians, sociologists, and other scientists confirm that the view of yesterday's family as a harmonious multigenerational unit that relied on mutual generosity and sympathy and was characterized by veneration of elders is largely a myth.

In preindustrial European agricultural settings, peasants commonly arranged through annuity contracts for the retention of certain property rights on the transfer of their assets to the next generation. Such legal documents often contained references to the right of the elder parent to continue to sit at the family table or to use the front door of the house.[2]

A somewhat different picture emerges from the world of crafts and trades. In this sector, the elderly commanded a certain degree of respect, but only insofar as they were able to contribute by passing on their knowledge to their sons. Even aging craftsmen and merchants strove for regulations regarding their very old age that would not impose their care and maintenance on their children. The fact that these individuals insisted on such written guarantees and regulations is testimony to their suspicion that their children might not accord them certain rights based merely on feelings of benevolence or veneration.[2]

In England before the year 1800, eighty percent of all persons 60 years of age and older were heading their own households. The tendency to preserve independence to the greatest degree possible was very strong, and the multigenerational household was not the usual expedient for the support of the aged.[2]

Industrialization, the effects of which were felt mainly by the urban working classes, cemented the separation between home and workplace. Although the family survived socially as a cooperative system, family economy came to depend on new and extended forms of production based increasingly on out-of-home occupational endeavors, effecting a decrease in the importance of traditional age roles.[2]

More recently, age-typifying social

From the Council on Scientific Affairs, American Medical Association, Chicago.

Report J of the Council on Scientific Affairs, adopted by the House of Delegates of the American Medical Association at the Annual Meeting, June 15 through 19, 1986.

This report is not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of the facts and circumstances involved in an individual case and are subject to change as scientific knowledge and technology advance and patterns of practice evolve. This report reflects the views of the scientific literature as of June 1986.

Reprint requests to Council on Scientific Affairs, American Medical Association, 535 N Dearborn St, Chicago, IL 60610 (William R. Hendee, PhD).

Members of the Council on Scientific Affairs are as follows: John R. Beljan, MD, Philadelphia, Vice-Chairman; George M. Bohigian, MD, St Louis; Stefano Bertozzi, Cambridge, Mass, Medical Student Representative; E. Harvey Estes, Jr, MD, Durham, NC; Ira R. Friedlander, MD, Chicago, Resident Representative; John H. Moxley III, MD, Los Angeles, Chairman; William C. Scott, MD, Tucson; Joseph H. Skom, MD, Chicago; James B. Snow, Jr, MD, Philadelphia; Richard M. Steinhilber, MD, Cleveland; Jack P. Strong, MD, New Orleans; Henry N. Wagner, Jr, MD, Baltimore; William R. Hendee, PhD, Secretary; William T. McGivney, PhD, Assistant Secretary. Staff authors are as follows: A. Harold Lubin, MD; Therese Mondeika, RD; Robert Rinaldi, PhD; and Valerie Vivian.

Table 1.—Published Classifications of Elder Abuse

	US Congress,[10] 1985	Kimsey et al,[20] 1981	Clark,[9] 1984	O'Malley et al,[13] 1983	Ghent et al,[22] 1985	Washington State Medical Association,[27] 1985	Hickey and Douglass,[21] 1981	Fulmer and Cahill,[23] 1984	Pearson,[25] 1986
Abuse									
Physical (active and passive)	x	x	x*	x†	x	x*	x*	x	x
Psychological	x	x	x	...	x‡	x	x§	x	x
Sexual	x	x	...	...	...	...	...	...	...
Exploitation									
Financial	x	x	x	...	x	x	...	...	...
Material	...	x	x	...	...	...	...	x	x
Neglect									
Active (physical)	x	x	x	x	...	x	x	...	x
Passive (psychological)	...	...	...	...	x	...	...	x	...
Self-neglect	x	...	...	...	...	...	...	...	x
Violation of rights	x	...	...	...	...	...	...	...	...
Medical	...	...	...	...	x	...	x	...	...

*Includes sexual abuse.
†Includes physical, psychological, and financial abuse.
‡Includes psychosocial abuse.
§Includes verbal/emotional abuse.

processes have militated against family unity and contributed to the distinction between life phases. Only within the past century has childhood been acknowledged as a separate life phase and accepted for its own value. Similarly for the aged, later life has become more distinctive as a special period. Compulsory retirement at a specified age, for example, has created a population of economically superfluous individuals. Federal programs that address special age-related needs (eg, Social Security, Medicare) have further strengthened the concept of distinct life phases.[8]

The formerly long and largely uncontrolled phase of procreation has shortened considerably in recent decades, leading to a prolongation of the "empty nest syndrome" (ie, the period extending from the time the last child leaves home until the death of one of the marriage partners). Simultaneously, largely as a result of modern medical technology, life expectancy has increased dramatically and old age has become accessible to more and more individuals, resulting in protracted periods of time during which the elderly are susceptible to physical pain and psychological deprivation. Finally, activity quotients concerning sociopsychological relations between the generations are changing, as the energies and emotions of younger adults are more occupied with concerns about their own life content than with obligations to and relations with older parents and grandparents.[8]

Definition/Classification

Although definitions and classifications of elder abuse lack uniformity, Table 1 demonstrates broad agreement in categorization of such abuse as physical (in one third of published studies, this includes sexual abuse), psychological, and financial and/or material. Less often is medical abuse or self-neglect indicated as a separate category. The explicit desire in most cases is to focus on the resolution of unmet needs, regardless of causal mechanisms.

Limitation of the concept of neglect to neglectful actions of caretakers is encouraged. Statutes addressing the phenomenon of self-neglect typically caution that "older persons are not children. Unless declared incompetent, they are responsible for themselves."[4]

According to the model bill known as the Elderly Abuse Reporting Act, prepared by the AMA Department of State Legislation:

> "Abuse" shall mean an act or omission which results in harm or threatened harm to the health or welfare of an elderly person. Abuse includes intentional infliction of physical or mental injury; sexual abuse; or withholding of necessary food, clothing, and medical care to meet the physical and mental health needs of an elderly person by one having the care, custody, or responsibility of an elderly person.[5]

Succinct guidelines that provide a practical listing of types of maltreatment (Table 2) have been published by the Washington State Medical Association.

Incidence and Prevalence

Abuse of the elderly is difficult to quantify because both the victim and perpetrator tend to deny it or downplay its seriousness. Often, the victim is overwhelmed by the abusive situation and either is embarrassed to acknowledge that he or she is being abused or does not know where to turn for help. Acceptance of the abuse and withdrawal from family and friends may follow.[6] In some families, a defensive posture is assumed and the problem is denied "to maintain family homeostasis."[7] Health professionals often minimize complaints of elder abuse because of disbelief, fear of accusing the perpetrator, or lack of awareness of the extent of the problem.

Results of studies that have examined the attitudes of medical students, physicians, and other helping professionals toward the aged have not been encouraging. In one study of first-year medical students, only 4% stated that they would prefer to treat elderly patients, while 48% stated a preference for working with younger patients. Interest in geriatric patients and geriatric medicine on the part of these students did not appear to be affected significantly by their knowledge of, attitudes toward, or personal contact with elderly persons.[8]

Deficiencies inherent in the identification of elder abuse victims notwithstanding, abuse of some type or combination of types has been estimated to occur in approximately 10% of Americans over 65 years of age,[9] and about 4% may be victims of moderate to severe abuse.[10] This means that one in every 25 elderly Americans (>1.1 million) may be victims of such abuse, representing an increase of approximately 100 000 abuse cases annually since 1981.[10]

If these estimates are accurate, elderly Americans are abused only slightly less commonly than children. Although one in three cases of child abuse is reported, this is true of only one in five cases of elder abuse. While the states spend an average of $22 per child for protective services, only $2.90 is spent for each elderly person. In fact, only 4.7% of the average state's budget is spent on protective services for the elderly (a drop of 2% since 1980), even

Table 2.—Classification of Types of Elder Abuse*

- **Physical or Sexual Abuse**
  - Bruises (bilateral and at different stages of healing)
  - Welts
  - Lacerations
  - Punctures
  - Fractures
  - Evidence of excessive drugging
  - Burns
  - Physical constraints (tying to beds, etc)
  - Malnutrition and/or dehydration
  - Lack of personal care
  - Inadequate heating
  - Lack of food and water
  - Unclean clothes or bedding
  - Lack of needed medication
  - Lack of eyeglasses, hearing aids, false teeth
  - Difficulty in walking or sitting
  - Venereal disease
  - Pain or itching, bruises, or bleeding of external genitalia, vaginal area, or anal area
- **Psychological Abuse** (vulnerable adults react by exhibiting resignation, fear, depression, mental confusion, anger, ambivalence, insomnia)
  - Threats
  - Insults
  - Harassment
  - Withholding of security and affection
  - Harsh orders
  - Refusal on the part of the family or those caring for the adult to allow travel, visits by friends or other family members, attendance at church
- **Exploitation**
  - Misuse of vulnerable adult's income or other financial resources (victim is best source of information, but in most cases has turned management of financial affairs over to another person; as a result, there may be some confusion about finances)
- **Medical Abuse**
  - Withholding or improper administration of medications or necessary medical treatments for a condition, or the withholding of aids the person would medically require such as false teeth, glasses, hearing aids
  - May be a cause of
    - Confusion
    - Disorientation
    - Memory impairment
    - Agitation
    - Lethargy
    - Self-neglect
- **Neglect**
  - Conduct of vulnerable adult or others that results in deprivation of care necessary to maintain physical and mental health
  - May be manifested by
    - Malnutrition
    - Poor personal hygiene
    - Any of the indications for medical abuse

*From the Washington State Medical Association.[27]

though about 40% of all reported abuse cases involve adults and abused elders.[16]

Both a recent cross-sectional survey of a variety of professionals[13] and a two-year study by the University of Maryland Center on Aging, College Park,[12] found that passive neglect is the most common form of elder abuse. Emotional and verbal abuse and active neglect (eg, abandonment, malicious withholding of required services, and financial exploitation) are less common, and violations of civil rights are rarely reported as long as care is perceived to be in the patient's best interest.

Research has indicated that rather than occurring as isolated incidents, abuse toward the elderly is frequent and recurring in up to 80% of cases.[15] The victim is typically a 75-year-old widow who has been forced to move in with a younger family member because her economic resources are insufficient to allow her to be independent.[4,15] Most victims also have at least one physical or mental impairment that necessitates care by others.[14] In fact, the elderly are known to have an average of 3.5 chronic diseases per person.[1] Elder abuse is found among all racial, ethnic, and socioeconomic backgrounds.[13]

The abuser is a relative in 86% of cases and lives with the elderly person in 75% of cases.[15] Approximately 50% of elder abusers are children or grandchildren of the victims, and about 40% are spouses. The average perpetrator has cared for the victim for 9.5 years; 10% have provided care for 20 years or more.[15] In over 60% of elder abuse case reports, the elderly person is a significant source of stress to the abuser. Physically apparent trauma is cited in over 50% of cases.[15]

Since estimates indicate that 60% to 80% of home care for the aged is provided by family members living in the same household, it follows that the family is the greatest source of elder abuse and neglect.[17] By contrast, only about 5% of the elderly population in the United States are cared for in institutions for the elderly.[18]

Etiology

Limited knowledge now exists from systematic, scientific investigation about the causes of elder abuse. The health care problems of the elderly, often more complex than those of other age groups, include physiological and metabolic changes, a higher incidence of disease, an increased prevalence of chronic illness, severe functional disability, and a higher incidence of multiple health problems.[19] The oldest of the elderly (those 85 years of age and older) are the fastest growing segment of the population. Furthermore, this cohort composes the frailest and most vulnerable group.[18]

In some instances of elder abuse, intentionality is evident. The following are examples from a recent report by the Subcommittee on Health and Long-term Care of the Select Committee on Aging, US House of Representatives:

- A 59-year-old woman less than 152 cm tall and weighing less than 45 kg was disabled by severe arthritis and other physical problems. On one occasion, her son hit her on the head with a board. On another, he picked her up and slammed her body into the ground.
- An elderly couple was persuaded to give a woman power of attorney over them in return for her moving into their home as their caregiver. In time, the couple was herded into a garage room while the woman lived in their home. Ultimately, they were sent to a nursing home. This woman stripped them of their home, car, and other assets, valued at $100 000.
- The son of a 65-year-old California woman confiscated her benefit checks and discarded her medications for arthritis and pain. He repeatedly demanded sexual gratification from her and threatened to throw her into the street if she made his practices known.[16]

In other cases, intentionality is not so apparent. The problem is complex and probably has multiple overlapping explanations. Most experts, however, appear to believe that a major precipitating factor is family distress.[18]

The following preliminary hypotheses have been proposed for elder abuse:

Dependency.—Abusive behavior may be triggered by the dependency relationship. As the elderly person must rely to a greater extent on someone else to provide services that can be withheld or omitted for reasons beyond his/her control, vulnerability to abuse and neglect is enhanced.

Evolving changes in the delivery of health care have increased pressure for shorter hospital stays and may result in early discharges of elderly patients. It is important to consider whether early discharge adds to home caretaker stress and contributes to elder abuse since these patients may require extensive care at home and, therefore, be at high risk for abuse.

Although the dependency per se may not be the sole explanation for abuse and neglect by caretakers, it may serve as a trigger by creating stress on the caretaker with maladaptive or inadequate coping mechanisms.[19] On conceptual and practical levels, dependency is closely linked to vulnerability.

Lack of Close Family Ties.—Failure to develop a strong relationship with the parent during childhood has been proposed to result in inappropriate responses to stress by the child, thus creating the potential for abuse and neglect.[20] In the absence of a close relationship between adult children and their parents, a dependent elderly parent can precipitate stress and frustration without the love and friendship necessary to counteract the new responsibilities of adult children. If the elderly parent has lived independently for a significant part of his or her life, the reunion with offspring might be viewed by the children as an intrusion, and abuse may follow.[20]

Family Violence.—Violence is a normal reaction to stress in some families, and it may continue from generation to generation.[9] The caretaker may have been abused as a child in an environment in which violence and neglect were the normal modes of behavior.[9] Thus, elder abuse may be a cyclic phenomenon, with parents and children mistreating each other throughout their lifetimes. Research is consistent in showing that abusive adults were victims of such behavior as children.[21]

Violence also may be precipitated by the unrelenting responsibility imposed on some caretakers. Many elderly persons, although probably a minority, become more difficult to care for as they age. They may be stubborn, untidy, and argumentative and may lose the higher-order psychological defense mechanisms acquired in earlier developmental stages. Some may become aggressive and even combative. Exhausted by the elderly person's progressive deterioration and seemingly insatiable demands, and overwhelmed by what appears to be a situation from which there is no escape, the caretaker may resort to violent behavior.[14]

Lack of Financial Resources.—With the demise of the extended family, many adult children find it difficult to care for aging parents. More middle-aged women, traditionally the principal providers of care to elderly parents, are seeking employment outside the home. And competent in-home help, when available, is very expensive.[22] When pressures mount on financial resources, as the need for potential caregivers to enter the work force intersects with the trend of an increasing older population in need of care, a view of the elderly parent as an economic burden may result, accompanied by a dramatic rise in the incidence and prevalence of elder abuse.

Although poverty or reduced finances may be a factor in family-mediated abuse of the elderly, it is not a sufficient cause, since elder abuse exists at all socioeconomic levels.[15]

Psychopathology in the Abuser.—Flawed psychological development of the adult caretaker has been suggested as the underlying or primary cause of mistreatment of the elderly, with the environmental contexts and situational problems providing the triggers or immediate causes of the acts of neglect and abuse.[23] Studies have shown that the person most likely to be cast in the role of primary caregiver for an elderly relative is often the least socially integrated adult child in the family (eg, one who is unmarried and unemployed).[16] Often, these individuals are beset with problems of their own, independent of the stressors placed on them by their elderly charges. In 63% of the cases of physical abuse studied by Hickey and Douglass,[11] the abuser was suffering from alcoholism, drug addiction, or psychosocial stress at the time of the abusive act.

Lack of Community Support.—Community resources generally are less available to the elderly person who is cared for by the family than to the isolated individual in the community. Lack of facilities to provide additional care for the elderly contributes to frustration and burnout in the caretaker and, thus, to the potential for abuse.[24]

Institutional Factors.—Primary attention has been directed to abuse from informal caretakers, since most of the disabled elderly rely on these individuals to meet their physical and personal needs. However, elder abuse also occurs in institutional settings (eg, nursing homes). Although many hypotheses proposed for abuse of the elderly by informal caretakers apply equally to formal caretakers, additional stressors may be operative in these settings.

Some observers have attributed abuse in the form of neglect in institutional settings primarily to low pay, poor working conditions, long hours, and the interference of paperwork and red tape with efficient care.[25] Abuse may occur for economic reasons as well. To cut costs, some institutions may provide food in lesser quantity and of poorer nutritional value, thus further diminishing the residents' quality of life. Additionally, medications designated for elderly patients may be misappropriated by employees for personal use or street sale.[26]

When to these factors is added the often pessimistic attitudes of formal caretakers that their patients will continue to deteriorate and die despite all efforts to the contrary, the result frequently is a callousness in which denial is employed as the chief psychological defense against a situation perceived as hopeless.[26]

Risk Assessment

The detection and assessment of elder abuse can be difficult. First, it is unlikely that abused elderly individuals would report acts of aggression against them by members of their families or by other caretakers on whom they rely for their basic needs. Second, to make an assessment, the physician and/or other health professional would have to gain access to the patient's home.

Although there is insufficient information to construct a clinical profile of the abuser, some observational guidelines have been developed that focus on the interaction between the elderly individual and the perpetrator in a home situation. A case detection approach may be helpful in identifying potential indicators of physical and behavioral abuse.[28]

Physical indicators have been described as "observable conditions of the aged person that range from signs of physical neglect to obvious physical injury"[28] (Table 2). The absence of assisting behaviors on the part of the caretaker, especially when verified by neighbors and/or relatives, also is indicative of abuse.

Certain types of behavior in elderly individuals provide information on the relationship with their caretakers. For example, excessive fear in the presence of adult children may indicate an abusive situation.[28] In assessing evidence of psychological abuse, one must keep in mind that what appears to be an angry, abusive exchange between the elderly individual and the caretaker may reflect a lifelong pattern of communication. In such instances, it would be necessary to verify one's suspicions with others who have known the individuals over a period of time.[28]

Elderly individuals at high risk for family-mediated abuse or neglect have been classified as those

- who live at home and whose needs exceed or soon will exceed their families' ability to meet them;
- whose primary caretakers are expressing frustration in dealing with care needs;
- whose primary caretakers are demonstrating signs of stress;
- who live in families with a norm of family violence;
- who abuse drugs or alcohol or live with family members who abuse drugs or alcohol or have episodes of loss of control;
- whose primary caretakers are under severe external stress (eg, loss of job, illness, or family problems).[19]

Assessment and recognition of these conditions may assist the health professional in identifying the potential for elder abuse. Additional factors to consider may include sudden deterioration of the elder's condition, coupled with caregiving of long duration or lack of assistance (financial and other types) from other family members or friends.[16]

The need exists for a concise, empirical assessment instrument that targets potential victims of elder abuse.[illegible] The fact that elderly persons most vulnerable to abuse and neglect usually have serious medical problems may serve as the basis for an ongoing assessment by medical personnel. Nurses appear to have gained access most successfully because of the reputation they have established as helping professionals.[illegible]

Barriers to Identification and Prevention of Elder Abuse

Paramount among the difficulties in addressing abuse and neglect of the elderly in the United States is the unwillingness of both those affected and of society in general to acknowledge that something so "alien to the American ideal" even exists. Many barriers thus represent gaps in knowledge: lack of information on the actual incidence and prevalence or number of persons affected; minimal systematic, scientific data on the causes of abuse in the elderly; no established procedures for case detection; insufficient knowledge about identifying and meeting the needs of elderly persons; incomplete data on either the potential victims of elder abuse or the likely perpetrators thereof; lack of empirical data on efficacy of psychosocial treatments and/or evaluation of intervention strategies; and difficulty in comparing outcomes of intervention activities among patient groups.

Further complicating the identification and prevention of elder abuse are existing societal norms: ageism or unfavorable attitudes toward older persons; disagreement on definitions of elder abuse; insufficient attention to the stresses inherent in caring for the chronically ill; poor delineation of appropriate family interactions to distinguish family violence from pathological elderly maltreatment; and perpetuation of the myth that, traditionally, families have been harmonious units that relied on mutual generosity and veneration of elders.

Additional factors that pose significant barriers to the reduction and elimination of elder abuse involve protection of individual rights of self-determination, privacy, and due process for both the abused and the abuser; inadequate societal resources to respond to identified cases of elder abuse and to deal with the abuser(s); wide variations among state statutes involved in identification and reporting of elder abuse; insubstantial and inconsistent local, state, and national empirical evidence; weak or nonexistent surveillance and enforcement efforts; lack of availability or coordination of services; risks of liability; lack of sound standards for state intervention; concerns about violating patient-clinic confidentiality; and, most difficult of all, an inability to determine the best ways to locate and identify the abused so as to intervene in a timely and effective way.

Concerted efforts to recognize these knowledge gaps and to acknowledge these defective societal norms and responses, to obtain the required information and to correct the inappropriate societal behaviors, should provide constructive assistance toward the prevention of elder abuse.

Intervention and Prevention

Elder abuse is a complex problem with dynamic and variable origins. While the preferred intervention is primary prevention, the current state of knowledge is not sufficient to make this an effective approach. Empirical data clarifying theories of causation must first be accumulated.

No one person or profession should be solely responsible for the management of these cases. Therefore, a multidisciplinary team of caretakers from the medical, social service, mental health, and legal professions should be utilized whenever possible. A multidisciplinary team is, by definition, a group of professionals and paraprofessionals from a variety of disciplines, often representing different agencies, working together to achieve a clearly specified set of goals. These goals may include coordination, diagnosis or identification, prevention, treatment, consultation, and education.

Multidisciplinary teams can be hospital, agency, or community based. To ensure adequate professional communication among team members and guarantee continuity of care for the patient, the multidisciplinary team must have a case manager. Any member can be selected to function in that capacity.

A typical team may be composed of a primary care physician, a nurse, a social worker, a psychiatrist, a psychologist, an attorney, a police officer, and a case data coordinator.[illegible] Although the composition of multidisciplinary teams may vary due to local resources, intervention programs should have access to homemakers/home health aides, visiting nurses, Meals-on-Wheels, transportation, emergency shelter, and legal aid, as well as medical and mental health services.[illegible]

The division of elder maltreatment cases into two broad categories, those elders dependent on caregivers and those not dependent on caregivers, may be useful for intervention purposes. In the case of an elderly person who is impaired and dependent on an abusive caregiver, the following interventions (which are not necessarily mutually exclusive) may be employed:

- provide in-house support services designed to maximize quality of care for the patient and minimize stress for the caregiver;
- provide respite care for the elder at regular intervals;
- provide supportive counseling and/or individual psychotherapy for the caregiver;
- explore permanent alternative living arrangements (eg, other family members, foster care, congregate living, or nursing home).[illegible]

In the case of an elderly person who is maltreated but not dependent on a caregiver, the following interventions (which are not necessarily mutually exclusive) may be employed:

- initiate legal action against the perpetrator (eg, obtain a peace bond or an order to vacate premises);
- provide in-home support services to the family to minimize opportunities for abuse;
- explore alternative living arrangements;
- provide necessary psychosocial interventions for the abuser (eg, individual psychotherapy, supportive counseling, and job training).

In all cases, intervention should promote the least restrictive alternative to ongoing maltreatment while respecting the personal rights of the elderly individual.[illegible] Before residential placement occurs, the following should be considered:

- what the patient wants;
- whose needs are being served by residential placement;
- whether all other alternatives have been explored.[illegible]

Although the primary goal of intervention is to protect the elder from maltreatment, it also may be important to recognize the needs of the perpetrator. In some cases, the caregiver is still potentially the most nurturing source of long-term care for the elderly person.[illegible] Supportive counseling provided to the abusive caregiver should include

- education regarding the etiology of elder abuse;
- assistance in clarifying and meeting personal needs;
- assistance in responding to any behavioral problems of the elderly person;
- assistance in maximizing the elderly person's abilities.

The first step in preventing elder abuse and neglect is to increase the levels of awareness and knowledge among physicians and other health professionals. Once high-risk individuals and families have been identified, physicians can participate in the primary prevention of maltreatment by making referrals to appropriate community and social service centers. Physicians may also participate by providing support and information on high-risk situations directly to patients.

Major management objectives for the physician involved in cases of elder abuse include the following:

- identify the elder who may have been abused and/or neglected;
- institute measures needed to prevent further injury;
- provide medical evaluation and treatment of injuries resulting from abuse and/or neglect;
- remain objective and nonjudgmental;
- attempt to establish or maintain a therapeutic alliance with the family (often the physician is the only professional who maintains long-term contact with the patient and family);
- report all suspected cases of elder abuse and/or neglect in accordance with local statutes.

Interventions that stabilize family-mediated abuse and neglect of elderly persons also may be effective in preventing maltreatment if applied prospectively. Physicians should encourage the development and utilization of supportive community resources that provide in-home services, respite care, and stress reduction within high-risk families.

Recommendations

The Council on Scientific Affairs recommends that:

- The AMA initiate the establishment of a multidisciplinary task force to develop approaches to intervention and prevention of elder abuse and to coordinate mutually supportive activities of various constituencies (eg, American Association of Retired Persons, American Nurses Association, American Public Health Association, American Hospital Association).
- Diagnostic and treatment guidelines concerning elder abuse and neglect be developed from the information contained in this report.
- The AMA organize a programmatic effort to address the national concern of elder abuse through state medical societies.

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Original Contributions

Assuring the Quality of Health Care for Older Persons

An Expert Panel's Priorities

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To select topics for quality assurance activities focusing on older patients, we convened a 14-member panel of physicians and experts in quality assurance. In two rounds of ratings, panelists rated 42 medical conditions (eg, pneumonia) in terms of their effects on patient outcomes, the availability of beneficial interventions, and the health benefits from improving current quality. They rated 27 health services (eg, adult day-care) on similar dimensions. The feasibility of doing quality assurance work on each condition and service also was rated. Using the ratings, the conditions selected for quality assurance work were congestive heart failure, hypertension, pneumonia, breast cancer, adverse effects of drugs, incontinence, and depression. Health care services selected were hospital discharge planning, acute inpatient care for the frail elderly, long-term–care facilities (intermediate-care facilities and skilled nursing facilities), home health care services, and case management.

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THE COST and quality of health care have become major national issues. For almost a decade, public and private agencies have debated the merits of differing methods of reducing expenditures for health care; recently, however, the discussions have paid increasing attention to preserving the quality of care. Because the elderly are major consumers of health care services, any discourse relating to the quality of health care in this country must consider the growing population of elderly patients.[1]

The US population is getting older.[2] The 12% of our population older than age 65 years accounts for over a third of the use of physician time, 25% of medications, and 40% of hospital admissions.[3] The quality of care given to older persons probably warrants improvement. Physicians tend to spend less time with older patients,[4] common geriatrics problems are frequently underreported or even undiagnosed,[5] and the medical care given to many nursing home patients is inadequate.[6,7]

Medicare's recent reliance on the prospective payment system and capitation to reduce costs has focused public attention on the quality of care given to older persons.[8] Some have argued that these policy initiatives may have an adverse effect on quality of care.[9] Not all agree, however, and instead, maintain that diagnosis related group incentives and managed capitated systems are preferable to the previous cost-reimbursement system.[10]

How might the quality of care for elderly patients be assured? One way is to make specific recommendations for the care of common medical conditions and the provision of health care services that are used by the nation's older population, the hope being that the availability of guidelines will favorably affect professional practice. This method is, in fact, being used by the Consensus Development Program of the National Institutes of Health.

Another way of assuring quality would be to evaluate formally the care given to older persons and take steps to remedy any deficiencies found. Guidelines for assessing quality have been promulgated by the American Medical Association.[11] These include the setting of explicit and implicit criteria for care by the professionals whose performance will be reviewed, prospective (as well as retrospective) studies, and reviews on a targeted basis (eg, specific diagnoses or services). This article describes how we attempted to identify such targets or topics for quality reviews.

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Table 1.—Medical Conditions Rated by an Expert Panel

- General
  - Immobility
  - Instability, gait disorders, and falling
  - Malnutrition
  - Decubitus ulcers
  - Sleep disorders
  - Adverse effects of drugs
- Cardiovascular
  - Congestive heart failure
  - Coronary artery disease
  - Valvular heart disease
  - Arrhythmias
  - Hypertension, diastolic and systolic
  - Hypertension, systolic alone
  - Hypotension, orthostatic
  - Abdominal aortic aneurysm
  - Peripheral arterial disease
- Pulmonary
  - Pneumonia
- Gastrointestinal
  - Dental disorders
  - Cholelithiasis and cholecystitis
  - Constipation
  - Carcinoma of colon
- Genitourinary
  - Urinary incontinence
  - Benign prostatic hypertrophy
  - Carcinoma of prostate
  - Urinary tract infections
  - Carcinoma of breast
  - Impotence
- Musculoskeletal
  - Osteoporosis
  - Hip fractures
  - Osteoarthritis of hips
  - Foot disorders
- Skin
  - Actinic keratoses and carcinoma
- Hematologic
  - Anemia
- Endocrinologic
  - Diabetes mellitus
  - Hypothyroidism
- Neurological
  - Parkinson's disease
  - Carotid bruits and transient ischemic attacks
  - Stroke
  - Syncope or presyncope
  - Dementia
  - Depression
- Special senses
  - Visual impairment
  - Hearing impairment

Table 2.—Health Care Services Rated by an Expert Panel

- Community based
  - Health screening
  - Geriatrics outpatient evaluation unit
  - Geriatrics primary care clinic (medical, dental)
  - Outpatient geriatrics rehabilitation
  - Outpatient preventive services (assessment, maintenance, health promotion)
  - Community mental health services
    - Social services center
    - Adult day-care (social)
    - Adult day-care (social-medical) (day hospital)
- In home
  - Home health care
  - Homemaker services
  - Home hospice
  - Physician services to homebound
- Institutional
  - Acute inpatient care geriatrics unit
  - Inpatient geriatrics evaluation unit
  - Inpatient geriatrics consultation service
  - Discharge planning
  - Hospice (freestanding, in hospitals, or in nursing homes)
  - Respite care
  - ICF or SNF*
  - Medical services provided in ICF, SNF, or congregate housing
  - Acute rehabilitation center
  - Psychiatric hospital care
- General
  - Primary care gatekeepers
  - Case management
  - Acute inpatient care, nonfrail elderly
  - Acute inpatient care, frail elderly

*ICF indicates intermediate-care facility; and SNF, skilled nursing facility.

METHODS

The Two-Round Panel Process

The project staff invited 14 physicians and quality assurance experts to serve on a panel. In selecting panelists, we attempted to achieve geographic dispersal and a balance between academic and private practice and between expertise in the care of older patients and quality assurance work. We prepared initial lists of 42 medical conditions (Table 1). We chose conditions that were prevalent and required special management considerations among older patients. We also prepared a separate list of 26 health care services for the elderly (Table 2). We mailed the lists of conditions and services and instructions for rating to the panelists. We also sent them background information on quality assurance methods, the prevalence of the medical conditions in the elderly, and the effectiveness of the health care services. The panelists rated each condition and service and returned their initial ratings by mail.

The panelists were subsequently convened and given a computer printout showing their individual ratings and the distribution of the entire group's ratings. After discussion, the panelists were asked to make their final ratings.

The Ratings

The panelists rated the importance of each medical condition and its feasibility for quality assurance work. Importance and feasibility each had three separate rating scales. An important condition was defined as follows: (1) one that is very often accompanied by significant adverse effects on outcome, such as mortality or loss of function, (2) one that has beneficial interventions (eg, medications, prosthetic devices, or surgery) available that can significantly affect outcome, and (3) one for which substantial benefit to health can accrue if current quality is improved. Each scale had five points. For example, the scale for the frequency of occurrence of significant adverse effects on outcome ranged from 5 (very often, or more than 50% of the time) to 1 (very seldom, or from 0% to 5% of the time).

We asked panelists to rate the financial feasibility of collecting reliable and valid measures of the structure, process, and outcome of care.[15,16] The structure of care was defined as its organization and administration (eg, the number of full-time physicians and nurses). The process of care referred to what is done to and for patients (eg, what laboratory tests are ordered and medicines prescribed). The outcomes of care were defined as the results of care (eg, changes in patients' functional capacities). Quality assurance work was defined as definitely feasible if analysis of existing or secondary data (eg, utilization records) would yield reliable and valid measures; it was considered of medium feasibility when new or specific data collection activities (eg, medical record reviews) were required; quality assurance was not thought to be feasible if it were very expensive and highly intrusive (eg, relying on face-to-face interviews with physicians or patients).

The rating format for health care services was similar to that used for medical conditions. Services were rated for importance, frequency of use, and feasibility for quality assurance work. Each of these categories had three scales. We defined an important service as one that is beneficial to the patient, is provided at a low level of quality, and is amenable to improvement. Panelists also rated the annual frequency with which each health care service will be used by older persons in the United States in the near future.

Statistics and Scales

We used the median as the summary measure of the 14 panelists' ratings because we wanted a statistic that could not be influenced by a few very high or low ratings. We used the mean absolute deviation from the median (an average of the deviation of each panelist's rating from the median) to measure the dispersion of the ratings. To assess change from the initial to the final round, we performed paired comparisons of the dispersion for each scale associated with the 42 conditions and 25 services that remained the same throughout the rating process. We treated the scales as interval scales because using statistics designed for interval scales on ordinal scales does not bias the results; by not using such statistics, information may be lost.[14]

Establishing Priorities

We set the following criteria for selecting medical conditions as priorities for routine quality assurance work: (1) high median ratings (4.0 or 5.0) for all three scales that comprised importance (occurrence of adverse effects on outcome, availability of beneficial interventions, and achievability of health benefit), and (2) high median ratings (4.0 or

5.0) for the feasibility of obtaining valid measures of either structure, process, or outcome.

Our criteria for selecting priority services were as follows: (1) high median ratings (4.0 or 5.0) for the benefit and improvability of the service, and low median frequency ratings (1.0 or 2.0) for its current quality; (2) a median frequency rating of at least 2.0 (use by more than 6% of people) for at least one age group; and (3) high median ratings (4.0 or 5.0) for the feasibility of measuring either structure, process, or outcome.

RESULTS

Medical Conditions

The panelists' final ratings indicated that, on the average, the combined list of specified medical conditions often had significant adverse effects on health outcomes (average median, 4.0), and that a moderate increase in health benefit could be expected if the quality of care were improved (average median, 3.1). The final ratings also suggested that obtaining information on structure, process, and outcome is probably feasible (average median ratings of 3.7, 3.7, and 3.6, respectively). The dispersion of ratings decreased significantly (*P*<.05) from the initial to the final round for all scales used to rate a condition's importance for quality assurance work and feasibility of obtaining valid measures of care.

Congestive heart failure, hypertension, breast cancer, adverse effects of drugs, and incontinence were selected as priorities (Table 3). Congestive heart failure, for example, met the criteria for importance because the panelists' ratings indicated that the condition was very often accompanied by significant adverse effects (median, 5.0), beneficial interventions to improve health are available (median, 5.0), and patients would benefit if the quality of care were improved (median, 4.0). Congestive heart failure also met the criterion for feasibility of obtaining valid measures of structure (median, 4.0), process (median, 4.0), or outcome (median, 4.0).

Some conditions met the criterion for feasibility but just missed doing so for importance. Decubitus ulcers and carcinoma of the colon, for example, received high ratings for the adversity they cause (median, 5.0) and the availability of beneficial interventions (median, 4.0); the panelists assigned lower ratings to the benefits patients would achieve if the quality of care for these conditions were improved (median, 3.0). No important conditions were eliminated as priorities for quality assurance activities because feasible measures of

Table 3.—Panel Median Ratings of Priority and Other Selected Medical Conditions

	Median Ratings					
	Importance*			Feasibility* of Measuring		
Medical Condition	Occurrence of Adverse Effects	Beneficial Interventions Available	Benefit Achievable	Structure	Process	Outcome
Congestive heart failure†	5.0	5.0	4.0	4.0	4.0	4.0
Hypertension, systolic and diastolic†	4.0	5.0	4.0	4.0	4.0	4.0
Pneumonia†	5.0	5.0	4.0	4.0	4.0	5.0
Breast cancer†	5.0	4.5	4.0	4.0	4.0	4.0
Adverse effects of drugs†	4.5	5.0	4.0	3.5	4.0	4.0
Urinary incontinence†	4.0	4.0	4.0	3.0	4.0	4.0
Depression†	5.0	4.0	4.0	3.0	4.0	3.0
Decubitus ulcers	5.0	4.0	3.0	4.0	4.0	4.0
Carcinoma of the colon	5.0	4.0	3.0	5.0	5.0	5.0
Valvular heart disease	4.0	4.0	2.0	4.0	4.0	4.0
Sleep disorders	2.0	3.0	2.0	2.0	2.0	2.0
Hypertension, orthostatic	3.0	3.0	3.0	3.0	3.0	3.0
Impotence	3.0	3.0	2.0	3.0	2.0	3.0

*Higher median ratings mean greater importance and feasibility of measurement on a scale of 5 to 1. Scales for importance are as follows: occurrence of adverse effects: 5, very often or more than 50% of the time to 1, very seldom or 0% to 5% of the time; beneficial interventions available, 5, definitely available to 1, definitely not available; and benefit achievable, 5, current quality is low and improving care would be beneficial to 1, care is already excellent or improving care would not be beneficial. Scale for feasibility is as follows: 5, definitely feasible to obtain reliable and valid measures to 1, definitely not feasible.

†Conditions chosen by the panelists as priorities for quality assurance work.

Table 4.—Median Ratings of Priority and Other Selected Health Care Services

	Median Ratings								
	Importance*			Frequency of Use*			Feasibility of Measuring		
Services	Benefit	Current Quality	Improvability	65-74	75-84	85+	Structure	Process	Outcome
Hospital discharge planning†	5.0	1.0	5.0	2.5	3.0	4.0	4.0	4.0	4.0
Acute inpatient care, frail elderly†	5.0	1.0	4.0	1.0	2.0	3.0	4.0	4.0	3.0
ICF/SNF†‡	4.5	1.0	4.0	1.0	2.0	3.0	4.0	3.0	2.0
Acute inpatient care, nonfrail elderly†	4.0	2.0	4.0	2.0	2.5	3.5	4.0	4.0	3.0
Home health care†	5.0	2.0	4.0	1.0	2.0	2.5	4.0	3.0	2.0
Case management†	4.0	2.0	4.0	1.0	1.0	2.0	4.0	4.0	2.0
Health screening	3.0	1.0	4.0	5.0	4.0	4.0	3.0	4.0	2.0
Homemaker services	4.0	1.0	4.0	1.0	2.0	2.0	3.5	3.0	2.0
Medical services in ICF/SNF	4.0	1.0	5.0	1.0	2.0	2.0	3.5	3.0	2.0
Respite care	4.0	2.0	4.0	1.0	1.0	1.0	3.5	4.0	2.5
Primary care gatekeeper	3.0	2.0	4.0	1.0	1.0	1.0	3.0	3.0	2.0

*Higher median ratings mean greater importance, frequency of use, and feasibility of measurement on a scale of 5 to 1. Scales for importance are as follows: 5, definitely beneficial to 1, definitely not beneficial; current quality, 5, definitely high to 1, definitely low; and improvability, 5, definitely yes to 1, definitely no. In the scale for frequency of use, the use of a service was considered least frequent if 0 to 5% of the defined population would use it, and most frequent if 51% or more would use it. Scale for feasibility is as follows: 5, definitely feasible to 1, definitely not feasible.

†Services chosen by the panelists as priorities for quality assurance work.

‡ICF indicates intermediate care facility, and SNF, skilled nursing facility.

quality were lacking. Several conditions, including sleep disorders, orthostatic hypotension, and impotence failed to meet any of the criteria.

Health Care Services

The panelists rated all specified health care services on average as probably beneficial (average median, 4.1), their quality average (average median, 3.2), and their quality probably improvable (average median, 4.1). The frequency of use was rated low for all three age groups. Obtaining measures of process and structure was rated probably feasible (average median ratings of 3.8 and 3.6, respectively). Obtaining measures of outcome for services was rated probably not feasible (average median, 2.5). The dispersion of ratings for health care services decreased significantly ($P<.05$) for all but one scale (benefit of services).

Hospital discharge planning, acute inpatient care for the frail elderly, and intermediate skilled care nursing facilities and home health care, and case management were identified as priorities (Table 4). Hospital discharge planning, for example, was rated highly beneficial (median, 5.0) and definitely improvable (median, 5.0), and its quality was considered definitely low (median, 1.0). In addition, the panelists' median ratings were greater than 2.0 for use of hospital discharge planning by persons in all age groups, and obtaining valid measures was considered financially feasible for structure, process, and outcome (all medians, 4.0).

Several other services met two of the three criteria. Health screening was considered of average benefit (median, 3.0), but met all other criteria for selection as a priority service for quality assurance activities. Homemaker services and medical services in intermediate-care facility/skilled nursing facility were rated important and frequent; however, measures of structure, process, and outcome were not considered financially feasible. Respite care was rated important and feasible but not frequently used. The lowest average ratings for quality assurance work were assigned to primary care gatekeeping services, which were of average benefit, had probably low but improvable quality, and were used infrequently by older persons.

COMMENT

In recent months, hospital-specific mortality rates for specific conditions have been used to describe the quality of care rendered to Medicare patients in various parts of the country (*New York Times*, March 12, 1986, p 1). While important, the interpretation of these data is limited because only a single outcome is considered. In this article, we describe how a national panel of medical and quality assurance experts selected potential topics for advancing routine quality assurance work for the population of older persons. By their ratings, the panelists indicated that this work can be expanded to include nonhospital settings, and that quality of care indicators other than mortality are feasible.

The merits of the panel's topics as priorities for quality assurance activities is contingent on the validity of the panel process. We choose one that has been used successfully to improve agreement among physicians.[15,16] Panel and rating processes are not without their critics,[17] however, and ours probably had flaws. Among them are possibly imprecise definitions of scales, medical conditions, and health care services, and the use of a five-point rating scheme. Also, other dimensions might have been included to assess a condition's or service's appropriateness for quality assurance activities. For example, concern for prevention of disease and impairment of function is implicit in many of the panelists' high ratings. Hypertension, breast cancer, the adverse effects of drugs, and urinary incontinence may be best approached through prevention. Hospital discharge planning, home health care, and case management share many preventive aims.

Despite the panel process' potential methodological limitations, the panelists came significantly closer to agreement after participation. Using their ratings, we were able to distinguish medical conditions that are important priorities for quality assurance work and for which valid measures of quality might be feasible to obtain; we were also able to discern health care services that are important, used frequently, and for which quality assurance work is feasible.

The panelists' choices are ready for consideration as targets for quality-of-care studies. A fundamental question is how to investigate them so that the findings accurately reflect differences in quality of care rather than differences in patient characteristics or severity of illness. The success of such studies will require substantial and thoughtful contributions from the clinical and research communities. The importance of assuring quality of care to elderly patients warrants making that effort.

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Item 5

American Society of
Consultant Pharmacists

2300 Ninth Street South
Arlington, Virginia 22204
(703) 920-8492

June 24, 1988

Chris Jennings
Senate Special Committee on Aging
Room G41 Dirksen Senate Office Building
Washington, DC 20510

Dear Mr. Jennings:

I have enclosed the position paper of the American College of Physicians (ACP), "Improving Medical Education in Therapeutics," which requests improved physician education in therapeutics, the treatment of diseases with drugs. The American Society of Consultant Pharmacists (ASCP) commends the American College of Physicians for taking this step and encourages and promotes improved communication between pharmacists and physicians.

We believe that emphasizing the multidisciplinary team approach and requiring drug therapy oversight activities, e.g. drug regimen review, in all care settings, nursing home, hospice, home health care and hospitals, will improve the professional milieu necessary to promote rational drug therapy and patient welfare.

The American College of Physicians "supports increased communication with pharmacists, as health care professionals with **particular knowledge in this area** [therapeutics]," (emphasis added).

We encourage and promote interactions between pharmacists and physicians to improve drug therapy through a variety of activities. Pharmacists in nursing facilities have documented the increase in patient quality of life and reduced costs through the drug regimen review process which identifies rational and irrational drug therapy. We are dedicated to providing the most efficacious drug therapy to the patient irrespective of the practice setting.

ASCP appreciates this opportunity to reaffirm our dedication to patient welfare through the rational use of medication.

Very truly yours,

Jay B. Farrar

Jay B. Farrar
Director of Government Affairs

Enclosure

Improving Medical Education in Therapeutics

HEALTH AND PUBLIC POLICY COMMITTEE*, AMERICAN COLLEGE OF PHYSICIANS; Philadelphia, Pennsylvania

MODERN MEDICAL EDUCATION has not dealt as effectively as it should with education of physicians in therapeutics. A traditional emphasis on the critical importance of correct diagnosis has not been followed by appropriate concern with the problems of therapeutics. Given the facts outlined below, this deficiency needs correction.

In the four decades since World War II, the United States has had a revolution in drug therapy. Even with the removal of more than 5000 products from the market as the result of the Food and Drug Administration's Drug Efficacy Study Implementation program, which was conceived in 1968, well over 8000 prescription drugs or combinations of drugs are now available in the United States. Old and familiar classes of drugs have expanded in size dramatically in this time. There are now at least 22 different penicillins available in the United States. The nonsteroidal anti-inflammatory drugs, (formerly the salicylates, phenylbutazone, and oxyphenbutazone) have been followed and largely supplanted by 11 new members of the class and a variety of new forms of salicylate salts. New classes of drugs such as the beta blockers and the cephalosporins, which were introduced by a single drug less than 15 years ago, now have become large families of agents. Seven different beta blockers are now available to physicians and their patients, and 15 different cephalosporins are now marketed in the United States. The development of new drugs is continuing and new classes of drugs such as the calcium channel blockers, angiotensin converting enzyme inhibitors, carbapenim antibiotics, and antiviral agents such as acyclovir continue to be introduced. In the United States today, a new chemical entity is approved for human use on the average of once every 2 to 3 weeks.

The number of prescriptions written in the United States has increased dramatically. Reliable estimates place this number in 1981 at approximately 1.3 to 1.4 billion, or 6.2 prescriptions for every person in the nation. In addition to absolute increases in the number of prescriptions written, the size of individual prescriptions has also increased. Between 1971 and 1981, the average size of a prescription increased by approximately 27% and the total amount of prescription drugs dispensed in the United States increased by 35% (1).

In the United States, approximately two thirds of all physician visits lead to a drug being prescribed (2). It has been estimated that a patient seeing a physician in the United States for a specific complaint receives approximately four times more medication than a person with the same complaint in Scotland (3). Whether this is reflected in improved health care remains to be established. In one study (4), 60% of physicians prescribed antibiotic treatment for the common cold. Studies (5-7) of antibiotic usage in hospitalized patients suggest that perhaps as many as 64% of antibiotic prescriptions in hospitals are either unnecessary or are for an inappropriate dose.

As drug use increases, adverse reactions to drugs can be expected to increase correspondingly. It has been estimated (8-10) that between 10% and 15% of all hospitalized patients have an adverse reaction to a drug during a hospital stay. While many adverse drug reactions are relatively minor and predictable occurrences, estimates of the frequency with which adverse drug reactions are the cause of hospital admissions have ranged from 0.5% to as high as 7.9% (8-13). In one study of 2499 hospital admissions, 4.1% were found to be due to adverse drug reactions. It was estimated that 27% of these admissions could have been prevented with more prudent drug therapy (12).

Unnecessary medical costs due to inappropriate drug use have not been calculated. However, given the evidence cited above, including the cost of excessive drug use, the recognized number of adverse reactions to drugs and the costs of hospitalization for treatment, and supplemental costs necessitated by such problems as acquired bacterial resistance to newly developed antibiotics, it is reasonable to conclude that the cost to our society is substantial.

The American College of Physicians recognizes that the "drug revolution" provides physicians with the opportunity to treat patients more safely, rapidly, and effectively than ever. To take full advantage of the potential benefits new developments in drug therapy offer to patients, and simultaneously to control the potential dangers these developments offer, the American College of Physicians recognizes the need for improved education of physicians and other health care professionals in rational therapeutics.

Positions

1. *The American College of Physicians supports increased education in therapeutics in medical school curricula and in-house officer training.*

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* This paper was authored by B. Robert Meyer, M.D. and was developed for the Health and Public Policy Committee by the Clinical Pharmacology Subcommittee: Paul D. Stolley, M.D., *Chairman*; David C. Lewis, M.D.; Victor Herbert, M.D.; Stuart L. Nightingale, M.D.; B. Robert Meyer, M.D.; William M. Bennett, M.D.; and Paul P. Carbone, M.D. Members of the Health and Public Policy Committee were Richard G. Farmer, M.D., *Chairman*; John R. Hogness, M.D.; Edward W. Hook, M.D.; Edwin A. Maynard, M.D.; Michael A. Nevins, M.D.; Richard B. Hornick, M.D.; Paul D. Stolley, M.D.; Charles E. Lewis, M.D.; John M. Eisenberg, M.D.; Malcolm L. Peterson, M.D.; Theodore C. Eickhoff, M.D.; and William L. Hughes. This paper was adopted by the Board of Regents on 26 June 1987.

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Virtually all formal pharmacologic education presently occurs in the second year of medical school, before significant exposure to clinical medicine. In this context, students are taught about drugs that are used to treat diseases with which they have only passing acquaintance, and have never actually seen in clinical situations. This often amounts to giving students solutions to problems they have yet to recognize exist.

While this early training in pharmacology is essential to medical education, subsequent education in clinical medicine needs to pay greater attention to inculcating in future physicians the basic principles and important facts necessary for rational therapeutics. This goal may be achieved by developing formal courses in clinical pharmacology and therapeutics in the last 2 years of the medical curriculum, or by incorporating more formal discussions of basic therapeutics into existing clinical programs. Students need to be taught in the clinical context about the rational use of drugs. This instruction should provide a familiarity with the clinical relevance of important pharmacokinetic concepts, an understanding of the need for individualization of drug dosage, an awareness of particular patient populations where drug therapy may be especially difficult, an understanding of the decisive importance of clinical trials for evaluating new therapeutic techniques, and a wise skepticism of pharmaceutical industry claims.

House officers are just as equally in need of educational programs in therapeutics. Frequently they are poorly informed about basic laws governing prescription and distribution of medications, and about basic elements of adequate prescription writing. The substantial majority of all drug orders in hospitals are written by these physicians. Reviews of hospital drug use show that hospitalized patients generally are treated with the most recent and novel drugs available. Of the 25 major drugs most frequently prescribed for hospitalized patients in 1983, only 5 had been available for more than 10 years (14). As has been noted, there is evidence that some of this usage is inappropriate. Like medical students, house officers need to continue to learn basic pharmacologic principles, further develop their ability to evaluate clinical trials, and gain a better understanding of the role of drugs in our society and in the physician-patient relationship.

2. *The American College of Physicians supports improved continuing medical education in therapeutics for practicing physicians, encourages the utilization of new techniques for providing physicians with timely information on drug efficacy and toxicity, and supports further research into optimal techniques for providing physicians with continuing education in pharmacology.*

The continued development of new pharmacologic agents mandates an emphasis on continuing pharmacologic education for the duration of a physicians' professional career. By the time a physician completes a 3-year residency program, it is usually 5 years since his course in pharmacology. In that interval, approximately 100 new drugs will have become available for his patients. Approximately 85% of all prescriptions written by senior physicians who graduated from medical school in 1960 will be for a drug about which they have received no formal education. Not surprisingly, reviews of prescribing practices of physicians suggest that the time at which they completed their speciality or subspecialty training is a critical factor in predicting their subsequent selection of therapeutic options (15).

After the completion of formal medical school and house officer training, there is no systematic exposure to intelligent, informative, and unbiased assessments of drug therapy. Continuing education in pharmacology occurs as the result of random encounters with a variety of information sources, including medical journals, the lay press, interactions with colleagues, and pharmaceutical industry sales representatives. The entire process can be characterized as largely random, incomplete, and subject to distortion.

Therefore, physicians should be provided with up-to-date and clinically relevant information concerning new experience with old drugs, the probable safety and efficacy of new drugs, and new advances in therapy. This information may be provided by means of informational bulletins, postgraduate medical education courses, grand rounds, or other activities. Increased dissemination of information concerning the activities of the Food and Drug Administration would also be particularly useful.

The College supports increased communication with pharmacists, as health care professionals with particular knowledge in this area. The use of hospital drug information centers staffed by pharmacists, and the use of computerized pharmacy programs concerning adverse drug reactions and potential drug interactions should also be expanded.

While recommending increased dissemination of information through these channels, the College recognizes that there is evidence to suggest that physicians respond poorly to written factual material distributed to them through normal channels. It appears that focused educational programs for individual physicians or small groups of physicians, programs that deal with specific issues in drug therapy, are more consistently successful (16-18).

In one study (16), direct discussion between a physician and a trained "detail" representative equipped with appropriate graphic and written material was the most effective way of affecting physicians' prescribing habits. Recent work (19) has described the effectiveness of a course in "clinical pharmacology" in improving the pharmacologic knowledge of graduating medical students. How such a course affects these physicians' actual use of drugs in their practice of medicine has not been described. How such a course might be adapted to the education of practicing physicians instead of medical students also has not been investigated. Further research is needed to clarify which techniques are best suited to the efficient distribution of information to physicians in a way that enhances their prescribing habits.

3. *The American College of Physicians supports new approaches to improving the understanding of drugs by*

patients and improved communication about medications between health care professionals and patients.

All patients are entitled to a full and thorough discussion of the benefits and potential risks of any medication prescribed for them. In addition, the face-to-face discussion with their physician may be usefully supplemented with other techniques for patient education. In some circumstances, this could involve discussion of the medication not only with the physician, but also with a nurse or clinical pharmacist with special training in this area. Many patients will benefit by the distribution of written material as a supplement to the information provided at the time of the office visit. Therefore, the College encourages its members to use the variety of informational material for patients developed by organizations such as The American Association of Retired Persons and the American Medical Association, as well as other organizations. Patients should be asked to read this literature at their leisure, and to ask their physicians any questions that are raised. Patients should also be encouraged at each encounter with a physician to discuss their medication and any adverse effects it may be producing.

American physicians prescribe more medication than their counterparts in other nations. While American physicians prescribe four times more medication than Scottish physicians, for example, few would defend the notion that Americans are four, three, or even two times healthier than their Scottish peers. Ironically, although physicians in this country prescribe a great deal, they also tend to express little optimism about the benefits of the medications they have given (4). In addition, some prescriptions serve purposes other than strictly medical ones. The prescription may be used by the physician as a signal to the patient that the visit has come to an end. It may also serve as evidence to both parties that the visit has been productive, and that the physician is "doing something" for the patient.

An essential aspect of improved drug therapy is a better understanding of how societal expectations of physicians and societal attitudes toward drugs influence the practice of medicine in the United States. Further research into this problem is needed.

4. *The American College of Physicians supports a systematic reevaluation of the relationship between the pharmaceutical industry, the practicing physician, and continuing pharmacologic education.*

While physicians uniformly deny that their understanding of drugs is influenced by the activities of the pharmaceutical industry (20-23), there is considerable evidence to support the efficacy of the personal encounter with a professional salesperson in shaping physicians' attitudes towards drugs. Avorn and associates (23) examined the opinions of practicing physicians in regard to three areas of drug prescribing, and found that the actual prescribing practices of physicians appeared to be heavily influenced by the views of the pharmaceutical industry.

The pharmaceutical industry may well be the primary source of continuing pharmacologic education for many American physicians. In this context, it is the responsibility of the pharmaceutical industry to support high-level educational programs for physicians that are separate and apart from their own marketing efforts.

Further research into the relationship of the pharmaceutical industry to patterns of drug utilization in the United States and to physician prescribing habits is needed. There is a need for formal guidelines of conduct for the College and its member physicians in their interaction with the pharmaceutical industry. Such a code of conduct has recently been adopted by The Royal College of Physicians (24). It provides detailed recommendations for the relationship of the profession to the industry and could serve as a model for guidelines for physicians in the United States.

► Requests for reprints should be addressed to Linda Johnson White, Director of Scientific Policy, American College of Physicians, 4200 Pine Street, Philadelphia, PA 19104.

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Item 6

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My name is C. Cecil Fuselier and I am a pharmacist. For the past 15 years my pharmacy practice has been in the area of geriatrics, as both an educator and as a practitioner. Currently I am an Associate Professor of Pharmacy Practice (Geriatrics) and Primary Preceptor for the Specialty Residency Program in Geriatrics and Long-term Care Pharmacy Practice at the College of Pharmacy, University of Arkansas for Medical Sciences. I have been in my present professorial position for the past 8 1/2 years. Prior to my present appointment, I held a similar position in geriatric pharmacy at the Assistant Professor level with the College of Pharmacy at Texas Southern University, Houston, Texas.

I am pleased to submit written testimony regarding the hearing: "Adverse Drug Reactions: Are Safeguards Adequate for the Elderly"? I would like to state at the onset that I do not submit this testimony as an official representative of the University of Arkansas, nor as an official representative of any national, state or local pharmaceutical organization or the profession of pharmacy, but rather my comments are to be interpreted as those of a concerned educator, clinical pharmacist and taxpayer.

My testimony will focus on the following 4 scientific and clinical concerns:

a) The need to educate primary care physicians on the special considerations important to drug prescribing for the elderly,

b) The need to educate pharmacists in the area of rational use of drugs in the elderly, geriatric patient drug education and the critical points of drug therapy monitoring in the aged,

c) The need for geriatric clinical studies and population statistic identification,

d) The need for enhanced awareness of sensory deprivation and subsequent medication education and labeling concerns.

As this committee is aware, a representative portion of this age group is quite health compromised. Although only 5 to 6 percent of the above 65 year-old population reside in nursing homes or other long-term care fecilities, this should not be interpreted as the remaining 94 to 95 percent is illness free. Quite the contrary, many are as ill as those in institutions or at least are at reasonable to high risk of becoming institutionalized. Many of these frail and ill elderly are cared for in private homes by aging spouses, their children, their friends and some live alone, caring for themselves. My experiences with ambulatory well, frail and ill elderly patients have made me conscious of some interesting facts. It is not uncommon to find ambulatory elderly health compromised because of:

1) The UNDER-USE of an appropriately prescribed medication.
2) The OVER-USE of an appropriately prescribed medication.
3) The MIS-USE of an appropriately prescribed medication. (the correct medication taken at the wrong time, with interacting foods or with interacting drugs [prescribed and/or over-the-counter products])
4) The NON-USE of an appropriate medication. (Non-use resulting from inadequate drug and/or disease information or because of unclear or non-readable label directions)
5) The use of an inappropriate agent chosen from an appropriate therapeutic category

There is a growing body of published data in geriatric medicine and pharmacy suggesting that gero-pathologies can alter the way elderly patients handle medications once they are ingested. Some of the most recognizable and predictable changes associated with aging can have significant impact on the:

a) absorption of medications from the stomach and intestines
b) distribution of the medication to vital organs and tissues
c) metabolism of the medication (how it is broken down so that it can be eliminated from the body
d) excretion or elimination of the medication

Age changes may slow or hinder drugs from getting into the blood. It is important for physicians to recognize age changes responsible for altering drug behavior such as absorption and be able to rationally select a product from the appropriate drug category. In other words identify a product possessing a more attractive profile of absorption when given to a compromised elderly individual.

The aging process appears to have effects on the distribution of certain drugs in the body. Some medications behave differently when given to overweight patients as compared effects seen when administered to lean or thin individuals. It is documented in the geriatric literature that the lean muscle mass/body fat ratio changes as we age. Elderly persons tend to lose lean muscle and accumulate adipose or fat. When certain medications, like some tranquilizers, are used in the elderly the medication tends to accumulate in this fat tissue and exhibits a longer duration of action as compared to the same drug used in the leaner, younger individual. If prescribers are not conscious of this aging characteristic an "average" dose may in actuality accumulate in the body causing an exaggerated or toxic effect.

The liver is a major site for drugs to be broken down once they have exerted there effect. This process (metabolism) is needed in order for the drug to be eliminated from the body. Many drugs are very dependent upon this process. The dose of the medicine suggested in many of the therapeutic references is based, usually, on a healthy or at least adequately functioning liver. Yet many older people have compromised liver systems disrupting the body's ability to handle "normal" or "average" doses. With adequate knowledge of these clinical and pharmacological points, prescribers are better prepared to alter the dose of medications in the elderly to compensate for these body system age changes. Our educational institutions should prepare physicians, pharmacists and nurses for practice in this specialized and complex setting.

More studies need to be done with older patients to clarify and highlight the effects that aging has on medication dynamics. We need to encourage physicians, nurses and pharmacists to observe more closely, record more frequently, document more clearly and report more often unusual drug responses seen in the elderly so that this body of knowledge can continue to grow. The day-to-day practitioner must rely on respectable scientific and clinical literature, clinical observations and judgment and continuing education efforts in order to keep up with this dynamic area of practice.

The best drug prescribed in the most appropriate manner has absolutely no benefit if the patient does not take it. The reasons for drug non-compliance are numerous. Expense of the medications is frequently cited as a reason for drug non-compliance. In addition to financial restrictions, non-compliance can be linked to a lack of patient drug and disease education. The problem of inadequate drug education begins as early as the visit to the physician. Many elderly patients have said that drug education is a responsibility of both physician and pharmacist. I sense from literature readings and personal experience that drug compliance is better in those individuals educated about their medical problems and about the medications used to manage those problems.

The College of Pharmacy at the University of Arkansas recognized some time ago the need to expose pharmacy students to the frail and ill elderly. By recognizing this importance a program was developed which required all senior pharmacy students to take a specialized clinical rotation in geriatrics and long-term care. This rotation introduces the student to the complexities surrounding the medical and therapeutic management of this population group. In addition, approximately 1 1/2 years ago, several faculty members from the colleges of medicine, pharmacy and nursing came together to establish an interdisciplinary geriatric team. This team actively practices and teaches geriatric practice skills to students from each of these colleges. The forum used by the interdisciplinary faculty is a geriatric ambulatory care clinic conducted on the Medical Sciences campus. From all indications, this approach has had a positive impact on medical, pharmacy and nursing students taking the rotation.

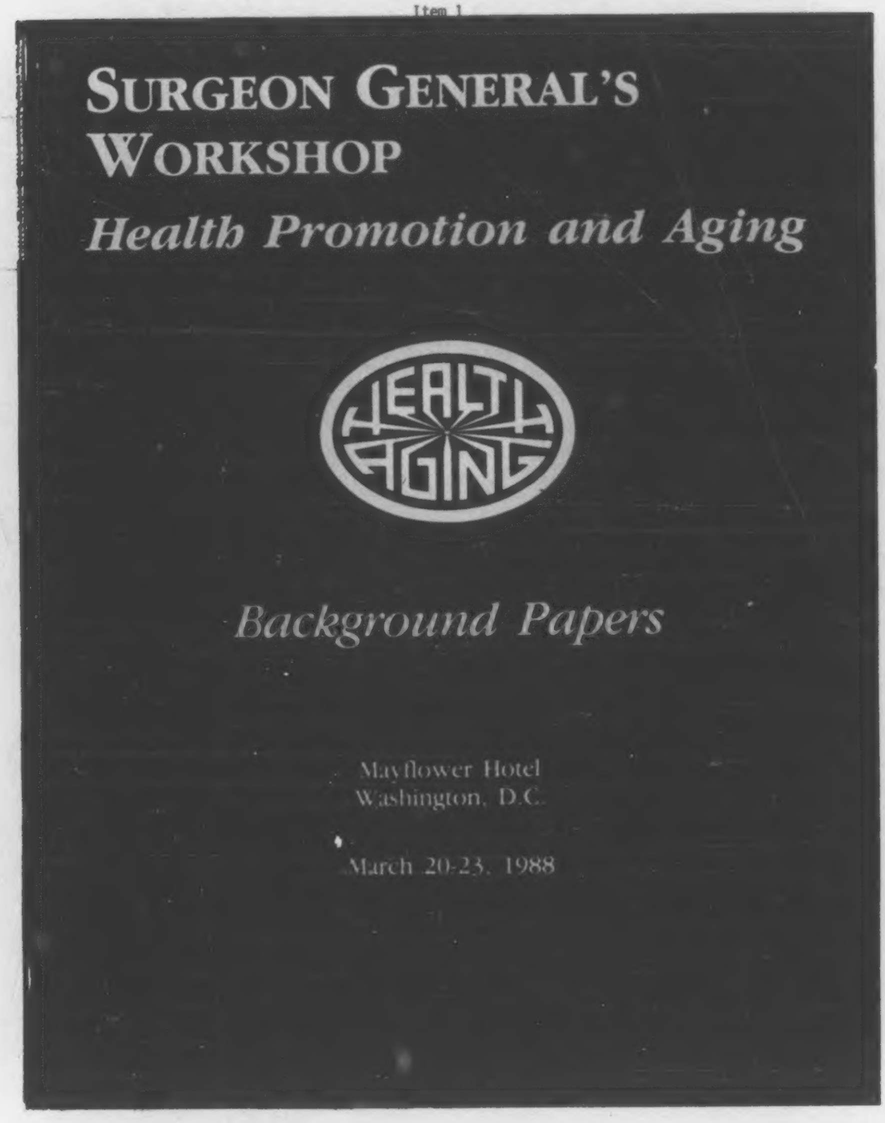
For the Committee: I solicit any and all help from national, state and local organizations that may be in positions to encourage physicians, pharmacists and nurses to train in the area of geriatrics. I feel that we as educators have an obligation to teach geriatric practice skills. I look to the system to help provide adequate motivation and resources to attract practitioners to this area of work. It must be recognized that some our elderly are ill **because** of our lack of geriatric practice knowledge and skills. This needs to be recognized, dealt with and corrected.

I appreciate the invitation to address this topic in this forum. I apologize for having to use clinical examples in my testimony. It is now best I can get my message across to my audience.

APPENDIX 4

BACKGROUND MATERIAL PERTAINING TO THE HEARING

Item 1



SURGEON GENERAL'S WORKSHOP

Health Promotion and Aging

HEALTH AGING

Background Papers

Mayflower Hotel
Washington, D.C.

March 20-23, 1988

THE FOLLOWING 14 PAGES CONTAIN

RECOMMENDATIONS

OF THE

U.S. SURGEON GENERAL'S WORKSHOP

ON

HEALTH PROMOTION AND AGING

MEDICATIONS AND GERIATRICS

MEDICATION INTRODUCTION

The panel recognizes that drug therapy is an essential component of preventive, as well as curative, strategies. It is the least expensive and most cost effective component of health care costs.

Optimal use of medication in the elderly requires certain reconceptualizations: the value of incremental improvement in functional status as an outcome measure and the therapeutic objective of maintaining the highest level of functioning at any given level of illness.

A new paradigm is needed which recognizes the patient as a partner with the caregiver in the use of medications.

MEDICATION EDUCATION

In the area of education, we recommend that:

1. health professional schools create an awareness of resources available for the prescriber, e.g., current geriatric text books in concert with PDR, USPDI, AMA-DE, and USHFS, to improve prescribing.
2. identifiable sites for prescribing information be available in all practice settings.
3. a different role for the pharmacist in geriatric medication--an expanded partnership with physicians as essential members of the care-giving team

4. patients be educated to keep their own medication profile including over-the-counter drugs.

5. programs are needed for the training of family, community, and other home-care providers in medication management.

6. prescribers, dispensers, and monitors of medication must understand age-related physiologic metabolic changes. Most important is decline in renal (kidney) function--the most frequently observed age-related change which can influence the use and safety of drugs that are excreted in the urine.

7. the gerontological community should be encouraged to become activity involved in the drug development process.

8. as a way of improving drug use in the elderly, all professional schools should include in the curriculum for all students' courses in the following areas:

   - non-judgmental patient counseling skills which recognize individual and cultural differences, and which recognize inherent ethnic differences, particularly in the use of nontraditional therapies;

   - interdisciplinary communication skills; and

   - basic concepts of epidemiology, pharmacology, and therapeutics, especially as relates to efficacy and risk of medications in the elderly.

9. a cadre of health professionals skilled in geriatric epidemiology and basic and clinical pharmacology must be trained.

In the area of service, we recommended that:

1. there be sustained, enhanced, and focused efforts to insure that older Americans have the information and tools they need (and have the right to expect) to be responsible partners in the medication enterprise.
    - the most effective tool for this is direct effective verbal communication, consultation and education regarding benefits, risks, and management of medication.
    - written information must be understood as a complement and not a substitute for dialogue.
2. third-party payors be encouraged to reimburse pharmacy services independent of the act of dispensing or the cost of the product. This includes such services as patient or provider consultation and witholding a prescription pending consultation with physicians.
3. alternative mechanisms of access to medicines for the geographically isolated and mobility impaired elderly. Study is needed of the potential limitations of such systems and the need for supported services, e.g., home health aids to encourage proper medication use and monitoring for side effects.
4. access to medicines and pharmaceutical services must be included as a basic part of broad health care programs for the elderly.
5. third-party reimbursement mechanisms must encourage (pay for) access to medical care appropriate for unique situations of complex medication regimens and isolated patients.

In the area of research, we recommend:

1. **research regarding the most cost-effective means of educating the consumer or the home caregiver regarding proper use of and monitoring for side effects.**

2. **research regarding standardization of the medication profile and drug interaction information in the computer software that supports medication profiling**

3. **research in the cost-effectiveness of medication profiling in the elderly.**

4. **research and evaluation regarding current and promising tools to improve the older Americans understanding and effective use of medications (compliance), e.g., medication diaries, color-coding, special packaging, large print and braille, pictographs, coordinated and consolidated dose forms, innovative delivery systems, easy-to-open packages, and messages adopted to social and cultural differences.**

5. **In the area of pharmacoepidemiological (post-marketing) research, we recommend:**

    - **post approval epidemiological research on elderly populations focusing on large automated linked data bases to study efficacy, risk, compliance, cost and new users rather than inefficient methods of ad hoc post-marketing surveillance, which require significant professional time;**

MEDICATION RESEARCH

- current potential data sets be explored, particularly those relating to the elderly, e.g., Medicare, AARP, VA, and TRIMI; the VAMP (England) automated medical practice model be examined as a possible model for use in the U.S.
- development of better drug utilization denominators to understand risks from adverse reaction signalling systems; FDA should publish their data for general use;
- targeted studies on nonlethal side effects to enhance patient acceptance and compliance and prevent secondary effects, e.g., dizziness, sexual dysfunction, nausea, incontinence, etc.; and
- in epidemiological research, greater clarity in definitions and measurement of outcomes and exposure.

MEDICATION POLICY

In the area of policy, we recommend that:

1. the standard of practice for pharmacists which includes use of up-to-date patient profiles and their application at the time of dispensing be endorsed.
2. consideration of medication provisions is vital in the Catastrophic Health Coverage Act (Medicare) (H.R. 2470) as follows:
    - Medicare should cover pharmaceutical benefits (prescribed items) including prescription and over-the-counter medication, biologicals, devices and appliances on an outpatient basis.

- State windfalls from Medicare assumption of coverage should be required to be redirected to the health benefits, including drug benefits, of the non-Medicaid poor and near-poor elderly.

- States should be permitted Federal matching funds for Medicaid programs providing medication services to elderly persons at 200% of poverty.

- so-called cost saving mechanisms in Medicare and Medicaid which control numbers or types of prescriptions or require co-payment for the poor and near-poor for medicines are potentially hazardous and ineffective and should be abandoned.

- correction of problems detected by drug utilization programs should emphasize education of professionals and not sanctions. Such efforts should be based upon current credible scientific indicators of medical practice and should focus upon direct professional and collegial contact.

- a new national mechanism is needed constituted by representatives of the gerontologic medication community for over-seeing and evaluating this effort.

3. pharmacological tools currently available need broader application to attack the major causes of illness, disability, and preventable death in the older American. The Federal Government should vigorously pursue and support research for the use of medications in National prevention strategies based upon the considerable success in hypertension. Fruitful current areas include: arteriosclerotic cardiovascular disease, congestive heart failure, diabetic complications, and osteoporosis.

- there is also promise in the longer term:
  - –protection of renal function;
  - –brain function and dementias;
  - –protection of connective tissues;
  - –preservation of immune function; and
  - –benign prostate hypertrophy.
- priority areas for treatment should also be directed to:
  - –chronic obstructive pulmonary disease (COPD);
  - –circulatory disturbances; and
  - –cognition restoration.

4. official governmental health agencies explore and expose fraud and quackery.

5. vitamins, certain food stuffs, and nutritional supplements which are being used as drugs be reviewed by appropriate regulatory agencies; regulatory changes be made.

6. new drug labeling include, where appropriate, directions for use in the elderly or other subgroups at risk. If no data are available, the labeling should state that data are not available.

7. for existing products, label statements regarding use in the elderly be added incrementally as the label is revised. A schedule for such reviews needs to be developed.

8. the use of official drug labeling as a patient teaching tool should be enhanced.

9. the FDA proceed with the final development and implementation of proposed guidelines for development of drugs for use in the elderly, especially elderly subgroups at risk; in particular, persons should not be excluded from clinical trials on the basis of age alone (ASCPT Workshop, December, 1986).

10. the Federal Government be a more active partner in the drug development process, both in establishing the basic science foundation and in other stages of evaluating drugs of importance for the elderly.

11. the Federal Government should restore the extramural programs of core support for population pharmacoepidemiologic resources.

12. emphasis should be placed on the development of cost effective strategies for incremental improvement of health status and maintenance of highest possible function through the use of medications for symptomatic relief of pain, sleeplessness, anxiety, depression, and problems of the preterminal state.

13. public exploration is needed of current policy, e.g., the orphan drug act, to stimulate the development of drugs, especially those without adequate profit incentive or with excessive liability concerns, e.g., non-patentable compounds, drugs off patent, vaccines, and orphan indication which could address unresolved problems in the elderly.

14. Post approval studies focusing on the aging population at risk.

Health Promotion and Aging
"MEDICATIONS AND GERIATRICS"

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I. Introduction and General Overview

Health promotion and disease prevention in the elderly is both appealing and worthy of our attention. While old age is not preventable, much of the disease and disability which is common in late life is preventable.[1] The rational use of medications, at both the policy and clinical level, has an important place in achieving this end, providing an important component in a health promotion strategy for healthy aging. Rowe and Kahn have cautioned against a "gerontology of the usual."[2] The focus on typical aging as "normal" ignores the enormous heterogeneity in this population. This may mislead scientists and policy makers to view what is "usual" as a reasonable health objective for older Americans.

II. Basic Demographics and Population Data

In 1987, about 12% of the U.S. population is 65-years or older. By 1990, the 65 and older group will reach 12.7% of the population; by 2000 the percentage rises to 13.1; and by 2020, to 17.5%. By the year 2020, the 65 and over population will have increased by 102%, compared to the 31% growth for the entire U.S. population for the same 40 year period.[3]

Changes will also be taking place within the elderly population itself. Not only will there be more citizens over 65 years of age, both in absolute number and percentage, but individuals within this age group will be living longer and, on the average, may tend to be more frail, and possibly in greater need of medical care. The older age groups, especially those over 75, will increase most dramatically. The current number of persons over 85 (2.7 million) will double by the end of the century. Conservative estimates to the year 2050 indicate that at least 50% of Americans will survive to their 85th birthday, with the 85 years and older population constituting at least 15 million people.[4]

III. Health Characteristics

Three general health characteristics of older U.S. residents are relevant to medications and geriatrics. First, the pattern of health service utilization influences the opportunities for receiving a prescription; second, the epidemiology of disease (especially chronic disease) influences the duration of treatment; and third, drug activity in the aging body influences therapeutic safety and efficacy.

A. Utilization of Health Services. Prescription drugs are prescribed for the elderly primarily as outpatients making physician office visits, as inpatients in long-term care facilities, and as hospitalized patients, as well as upon discharge from health care institutions. Persons 65 and older account for 20.5% of physician office visits in 1985.[5] And while most elderly are not in nursing homes, they did occupy 88% of the available nursing home beds in 1985.[6] And in 1986 persons 65 and older accounted for more than 40% of the hospitalizations in this country, staying an average 8.5 days compared to 6.8 days for 45-64 years of age.[7] "In the near future, the majority of all users of health and health related services with the exception of obstetrics and pediatrics will be persons over 65."[3]

B. The Epidemiology of Disease. As briefly discussed above, the elderly in America are more likely to use health services than are younger age groups.[8] This is explained in part by the fact that in spite of fewer acute illnesses, their recovery time is often longer; the fact that they are nearly twice as likely to suffer from a chronic illness; and the possibility that they may overuse services relative to true need.[9,10] In view of this reality the health care system's response requires strategies that are often quite different than those for younger persons because of the following:

the prevalence of chronic disease. Eighty percent of persons 65 years and older have one or more chronic diseases. Certain of these diseases are largely age dependent, such as coronary artery disease and dementia of the Alzheimer's type; other diseases, such as most cancers, are considered age related.[11]

multiple pathology. The existence of several simultaneously active conditions is much more prevalent in the aged than in those younger.

nonspecific presentation of disease. Several diseases which occur at all ages have a different natural history in the elderly. Almost any of the classic signs or symptoms of disease are present in the elderly in uncharacteristic ways. Instead of usually anticipated presentations, diseases often give rise to nonspecific problems which may be incorrectly identified as due to aging rather than due to disease. These nonspecific problems include falling, dizziness, acute confusion, new incontinence, weight loss, failure to thrive, etc.

silent presentation of disease. Especially likely to be obscured in the elderly are pulmonary embolism, pneumonia, cancer, acute surgical abdomen, thyrotoxicosis, depression, drug intoxication, myxedema, myocardial infarction, alcoholism.[12,13]

C. Pharmacokinetics and Pharmacodynamics of Drugs. Drug disposition in the body of an elderly patient may be quite different than in a similar patient forty years younger. Although these changes may not necessarily occur, when present they are largely the result of age related changes in body composition, renal and hepatic function, and concurrent disease states. In addition, an older patient may not respond to a given drug concentration in the same manner as a younger individual.[14,15] Age related physiologic changes in older patients dictate that while the standard guidelines for applying pharmacokinetic principles often apply, they must be approached with caution because some of the usual assumptions may not be valid. In particular, the clinician must more carefully consider possible changes in body composition and vital organ function.

ABSORPTION / A number of aging-related physiologic changes occur in the gastrointestinal tract (GI) which increase the possibility of altered drug absorption. With advancing age intestinal blood flow may decrease; muscle tone and motor activity in the GI tract may decline; and mucosal cells may have atrophied, reducing both gastric secretory and absorptive function. The elderly demonstrate prolonged and widely variable gastric emptying times when compared to younger groups.[16] In addition, the pH of GI fluid is increased in the elderly, a change that may effect the absorption of calcium.[17] in spite of these demonstrated and theoretical GI changes, altered absorption does not appear to be a clinically important factor in dosage calculations for older patients.[18]

DISTRIBUTION / Body composition undergoes noteworthy changes over a lifetime of 70+ years. Body fat increases, muscle mass decreases, and total body water decreases. By age 70 greater than 30 percent of body weight in a given individual may be fat. On the other hand, muscle mass contributes a smaller proportion of body weight, declining by an estimated 25 to 30 percent by age 70. Total body water decreases in the elderly from 13 to 18 percent.[19,20] These changes can have a clinically significant impact on the distribution of both water soluble and lipid soluble drugs. As a rule, with substantially increased age, water soluble drugs will have decreased distribution, while lipid soluble medication will have increased distribution.

The plasma protein binding of drugs in the elderly may be altered.[21] The two major plasma proteins are albumin and alpha-1-acid glycoprotein. Older patients often have a lower than normal serum albumin level, usually the result of decreased albumin production. Also, an increased level of alpha-1-acid glycoprotein has been associated with advanced age.[21] The potential significance of these changes are either an increased free fraction of drugs bound to albumin (e.g. warfarin, phenytoin) or decreased free fraction of drugs bound to alpha-1-acid glycoprotein (e.g. lidocaine, propranolol). These alterations in binding may lead to the erroneous clinical judgments based on misinterpretation of serum blood levels.

METABOLISM / Phase I oxidative metabolism can be impaired in the elderly patient due to decreased microsomal enzyme activity. Also, the metabolism of drugs with high hepatic extraction ratios can be impaired due to a decrease in hepatic blood flow.[22] This is particularly important when prescribing certain drugs such as diazepam, quinidine, theophylline, propranolol, and imipramine. Easily estimating the extent of impaired metabolic function is not currently possible; consequently, dosage adjustments necessitated by metabolic impairment are, at best, estimates based on investigational and clinical experience.

Hepatic Phase II metabolism via conjugation is not meaningfully altered with advancing age. Consequently age related changes in clearance of drugs metabolized by glucuronidation clearance have not been reported. For example, oxazepam, lorazepam, and temazepam doses need not be reduced in older patients on the basis of hepatic function alone.

ELIMINATION / Glomerular filtration rate (GFR) declines steadily with increasing age. Because of the typical decline of muscle mass with advancing age, production of creatinine also declines. This produces serum creatinine levels usually considered normal for younger persons, but unreliable as an indicator of renal function in the older person. Thus, a calculated creatinine clearance is recommended when considering the proper dose of such drugs as digoxin, cimetidine, many antibiotics, and active metabolites such as N-acetylprocainamide and normeperidine.[23,24]

PHARMACODYNAMICS / The term pharmacodynamics usually refers to the magnitude of pharmacological effect that results from the interaction of drugs with receptors at the site of action. There is little information about the pharmacodynamics of drugs in the elderly, but an increased "sensitivity" to a number of drugs has been reported.[20,25] Perhaps the most widely reported is the enhanced pharmacological effect of narcotic analgesics in the elderly.[26,27] In a study by Kaiko it was found that elderly cancer patients, who received intramuscular morphine post-operatively, had significantly greater total pain relief and duration of pain relief than their younger counterparts. No information regarding adverse effects was reported.[28] This study confirmed similar findings reported in an earlier study by Bellville, et al.[29] Demonstrating decreased pharmacodynamic sensitivity, Vestal et al. have reported a reduction in response to both beta adrenergic agonist and antagonist drugs in the elderly.[30] From these and similar reports there is some evidence that age-related pharmacodynamic changes can occur. For the most part whether these alterations are due to diminished homeostatic mechanisms, chronic disease, or changes at the receptor or post-receptor remains to be determined.[20,26]

IV. Areas of Particular Interest

Medications are usually beneficial, sometimes of no value, and on rare occasion detrimental in their contribution to the health of the elderly. Numerous areas are of particular interest with regard to drugs for older patients. The few areas discussed in this background paper are the extent and pattern of drug use among older patients; the health promoting benefits the elderly derive from medications; their susceptibility to untoward effects of drugs; the potential for new technologies to benefit the elderly; successful interventions and programs; and selected deficiencies in current programs and services.

A. The Extent of Drug Use. The elderly take prescription and non-prescription drugs to a greater extent than younger persons. This appears to be so because their greater use of health services makes them more likely to receive prescriptions or make self-medication decisions.

PRESCRIPTION DRUG USE / As previously mentioned, the elderly make up 12% of the U.S. population. It is estimated however that this group accounts for approximately 30% of all drugs prescribed in the U.S.[6,31] In 1982 all consumers spent $14.5 billion for prescriptions dispensed by community pharmacies.[33] The elderly's precise proportion of that cost is not known, but if it was 30% that would be $4.35 billion. An FDA study found that those over 75 years of age received the most prescriptions in 1982, averaging almost 17 annually. The "young-old," those 65 to 74, received only 13.6 that year. These numbers are much larger than the averages of those in the 55 to 64 age group (9.3 prescriptions) and the 45 to 54 age group (6.9 prescriptions).[33]

The 1985 National Ambulatory Medical Care Survey of office based physicians found that elderly women accounted for 12.5 percent of all visits and 17.7 percent of visits in which drugs were prescribed; elderly men accounted for 8.0 percent of visits and nearly 11 percent of visits involving drug prescription.[33] Overall at least one drug was prescribed or provided in over 68 percent of office visits by those 65 years of age and older.

OTC DRUG USE / Self medication as part of self-care seems to be one of the most important and frequent health maintenance actions taken by the elderly. A recent study of rural elderly found 65% of those surveyed to have used over the counter (OTC) medications in the previous two weeks, with women taking more than men.[34] This was consistent with findings from an earlier study of an elderly population in which 64% had taken OTC medications; again, women used more than men.[35] Respondents in this study reported consuming in a one day period an average of 1.74 prescription drugs and 1.13 over-the-counter drugs.[34]

B. Patterns of Drug Use. Drug use patterns in the elderly vary according to the populations in which data is collected. The best defined data comes from ambulatory elderly populations. Two ongoing programs, the Dunedin Program in Florida and the N.I.A.'s Established Populations for Epidemiologic Studies of the Elderly (EPESE), provide the most extensive and detailed information about both prescribed and OTC medications in a controlled study population or cohort. The Dunedin Program which has screened approximately 3,000 elderly each year since 1978 for undetected medical disorders, has also collected patient-recorded information about prescribed and OTC medication. Over a five-year period 93% of patients in that population took some medication, with a mean of 3.7 medications at the time of interview. The study also found women to be consuming more than men, and drug use increasing with advancing age.[36] The most common therapeutic indications for all drugs were antihypertensives, non-narcotic analgesics, antirheumatics, various vitamins and cathartics. Striking changes over the five year period include an increase in mean drug use (from 3.2 medications) and a considerable increase in nutritional supplement use.[36]

The EPESE project, a community-based surveillance program funded by the National Institute of Aging, is being conducted at four research sites; New Haven (Yale University), East Boston (Harvard University), rural Iowa (University of Iowa), and the Piedmont area of North Carolina (Duke University). Extensive information regarding both prescription and OTC medication use is being collected as part of these in-home surveys of between 3,000 to 4,500 community elderly. The first published report of medication use in an EPESE population was from Iowa where 88% of patients took some medication, with the mean being 2.87 drugs. In this population medication use increased with age and was greater in women.[34] The most common therapeutic indications for drugs were cardiovascular, analgesics, vitamins and nutritional supplements, gastrointestinal products and CNS agents. Analgesics, vitamins, and GI agents (e.g., laxatives) were the most frequently taken over-the-counter therapeutic categories in Iowa among rural elderly.[34] In fact, products classified as "analgesics and antipyretics" constituted over 39% of the reported OTC drug use; and three most frequently mentioned categories accounted for more than 94.1% of this use. While the Dunedin and Iowa populations and methods are not comparable, the most distinguishing difference is the apparently greater use of drugs seen in the Florida population.

Additional information about commonly prescribed medications for ambulatory elderly comes from a variety of sources. The most recent information (1986) is from two electronic data bases: IMS America Ltd. (Ambler, PA), and Pharmaceutical Data Services [PDS] (Scottsdale, AZ).[37,38] The top five therapeutic classes prescribed for the elderly according to the IMS data were digitalis preparations, diuretics, beta-blockers, nitrates, and antiarthritics. The PDS data, reflecting prescription drugs dispensed, showed the top five drugs for the elderly to be hydrochlorothiazide and triamterene, digoxin, potassium chloride, nitroglycerin, and furosemide.

Drug use patterns from institutional settings are less well defined. A 1976 survey of long-term care facilities found that most patients received between 4 and 7 medications with the mean being 6.1 drugs.[39] The most common therapeutic indications were cathartics, analgesics, tranquilizers, sedative/hypnotics, and vitamins. According to PDS, the top five drug products dispensed to elderly nursing home residents in 1986 were digoxin, furosemide, potassium chloride, dipyridamole, and nitroglycerin.[38] This pattern reasonably reflected the frequency of use these products had among non-institutionalized elderly that year. In alarming contrast, the sixth and seventh ranking drugs among elderly nursing home residents were haloperidol and thioridazine HC1; among non-institutionalized elderly these same agents ranked 99th and 90th respectively.[38] This report also revealed that during the first quarter of 1986, 59.2% of the elderly in the nursing homes received 4 or more prescriptions, compared to 35% of the non-institutionalized elderly.

Drug usage in hospitalized elderly is available from a variety of sources. A drug use surveillance project on a geriatric specialty unit found 500 of 521 patients to be given medications. Patients observed during the study period were given an average of 6.1 medications. In order, the most frequently used drugs were diuretics, antibiotics, bronchodilators, and analgesics.[40] Another study of 56 hospitalized elderly patients reported the mean drug use to be 4.1 medications prescribed for chronic use with the most common therapeutic indications being cathartics, analgesics, vitamins, diuretics, and cardiac drugs.[41]

C. Health Promotion Benefits of Drug Therapy. Health promotion strategies, particularly in older populations, must clearly rely on both social-behavioral and medical strategies. Many maladies of old age can be traced to health risk behaviors of young adulthood, and as a result prevention is often viewed as having little value as a health strategy after 65 years of age. Kannel and Gordon have suggested "that because of the relatively high incidence of mortality in the elderly the absolute impact of preventive measures short-term may actually be greater in the elderly than the younger despite a lesser relative impact."[42]

Since that suggestion, made in 1977, the preventive value of treating diastolic-systolic hypertension in the elderly has been demonstrated. The V.A. cooperative study demonstrated a 54 percent reduction in fatal and nonfatal cardiovascular events in the 60 years and over age group.[43] The Hypertension Detection and Follow-up Program found that older patients receiving drug therapy according to structured guidelines (otherwise termed "stepped-care") had lower incidence of stroke and lower mortality than age matched controls referred to their usual "regular care" for management.[44] And, results from the European Working Party on High Blood Pressure in the Elderly Trial have shown dramatic reductions in morbidity and mortality among drug treatment subjects over a seven year period.[45] Of course the importance of attentive monitoring during treatment cannot be over emphasized; anti-hypertensive medications are among the most widely implicated contributors to adverse drug reactions in the elderly [reviewed later in this paper].

The efficacy of influenza vaccine was evaluated in nursing homes of Genesee County, Michigan, during the winter of 1982-83. Investigators found the use of influenza vaccine to reduce both incidence and severity of influenza virus infections among the elderly.[46] A positive cost-effectiveness analysis of influenza vaccination programs for the elderly was reported comparing medical costs and health effects between vaccinated and unvaccinated elderly from 1971-1972 through 1977-1978.[47] Despite belief in the preventive value of the vaccine, medical compliance with recommendations for its use has been poor; institutional policy appears to be the best means for accomplishing wide spread immunization.[48]

Disability and immobility are associated with fractures in older persons; and fractures are associated with low bone mass.[49] The N.I.H. estimates that about 1.3 million fractures a year can be attributed to osteoporosis in people aged 45 years and older.[50] As one of the most prevalent afflictions of advancing age, osteoporosis-related vertebral fractures burden one-third of women by age 65. By age 81 hip fractures, usually associated with osteoporosis, will have stricken one-third of the women.[51] An effective means of preventing the loss of bone mass in postmenopausal women is regular use of estrogen therapy, particularly when combined with calcium supplements.[52,53,54] The FDA recently acknowledged this preventive indication to be an effective use of estrogens when taken for 21 or every 28 days and combined with calcium supplements and exercise.

A variety of useful but less well documented preventive and protective actions of drugs have been reported. For example, a case-control study of 300 cataract patients and 609 controls found a protective effect from long-term use of aspirin-like analgesics.[55] Such findings clearly require methodologic scrutiny and additional investigation. But they also ought to encourage the continuing search for agents with potential for preventive/protective impact on common disabling conditions of advanced years.

D. Health Risks and Problems Associated With Medications. The major areas of concern with regard to health risks and problems associated with geriatric drug therapy can be organized as bio-medical, behavioral, economic, and health policy/health services. Conversely, these areas also represent important targets for drug oriented health promotion interventions. In general, issues reviewed independently in this background paper (e.g. adverse drug reactions, compliance, costs, access, and attitudes) are very much interdependent, and an integrated approach to solutions is recommended.

DRUG RELATED BIO-MEDICAL ISSUES / Aging is associated with a variety of physical changes and health problems. Adverse drug reactions also present in a wide variety of symptoms throughout the body. A major challenge for the clinician is to distinguish between symptoms of aging and those associated with drug therapy. Mental disturbances, fatigue, depression, and syncope are examples of complaints that are associated with commonly encountered conditions as well as frequently prescribed medications.[56]

1. THE EPIDEMIOLOGY OF ADRs. Just as drug use patterns vary with populations, incidence and prevalence data for adverse drug reactions (ADRs) is quite dependent on data collection methods and settings in which studies have been conducted. Multicenter collaborative drug surveillance programs, voluntary reporting to FDA, cohort surveillance, the control phase of intervention demonstrations, institutional or population specific prevalence surveys, and computerized record linkage of secondary data sets have provided the most enlightening perspective on ADRs in the elderly thus far.

The Boston Collaborative Drug Surveillance Program (BCDSP) formalized and standardized clinical data collection on medication use and effects in a consortium of hospitals. Routine screening procedures have been used by BCDSP to correlate patient factors and drug response. From this effort dozens of adverse effects associated with drug therapy have been identified; advanced age has been an important variable in several instances (e.g. heparin in older women[57] and high dose flurazepam in older patients[58]).

The FDA has been collecting reports of suspected and known adverse drug reactions (ADR's) since 1968. The data has limitations because of the spontaneous and voluntary nature of the reporting system. Nevertheless, the value of summary information from this data set to alert researchers and clinicians to drugs worthy of more careful attention should not be overlooked. Recently FDA data from the 15 year period 1968-82 was tabulated to identify medications which may cause the older patient untoward effects.[59] From this analysis the five generic drug classes with the highest reported adverse drug reactions were identified. These were, in order, antiparkinsonian drugs, antibiotics, antiarthritics, antiarrhythmics and diuretics. The most recent data from FDA spontaneous reporting indicates an overall rate of 8.5 ADR reports per 100,000 population; the rate among those 65 and older is nearly double that.[60]

Drug induced admissions to hospital were examined along with other iatrogenic causes of hospitalization at a 769-bed urban teaching hospital.[61] In that institution 4.2% of admissions during two summer months were attributed to medication; half of which were considered by the investigators to be potentially avoidable. Medications accounted for 77% of all iatrogenic admissions. The average age among all iatrogenic admissions was 55 years. Another report of 293 admissions to a family medicine inpatient service found 15.4% to be drug-related with almost one-half occurring in patients 60 years of age or older.[62]

The occurrence of ADRs during hospital stays provides another perspective. During March and April of 1981 records for all admissions to Denver's VA Medical Center were reviewed.[63] In this study the occurrence of hospital associated iatrogenic complications for veterans aged 65 and older was compared with younger patients. The younger group had no complications caused by drug reactions while 17.7 percent of the older group experienced an ADR. This rate is consistent with those reported in other studies.[64,65] The differences between hospitals are perhaps due to the use of different criteria for determining a drug reaction.

Growing awareness of aging has stimulated an increasing number of investigators to use large computerized data sets to focus on drugs for their possible etiologic part in common problems of old age. Two examples for illustrative purposes are included. (1) An association between psychotropic drug use and hip fractures has been identified using computerized Medicaid files; dementia as a confounding variable did not appear to influence the results.[66] (2) A slightly increased risk of hospitalization because of gastrointestinal bleeding has been noted among elderly users of nonsteroidal anti-inflammatory drugs compared to nonusers at the Group Health Cooperative of Puget Sound.[67]

3. FACTORS CONTRIBUTING TO ADRs. It's estimated that at least 60 percent of adverse drug reactions are an extension of normal pharmacologic action.[68,69] Because most adverse effects are pharmacologic and usually well-known minor reactions, many should be preventable with more careful prescribing, monitoring, and patient education.

Elderly patients are at a higher risk of developing drug reactions than the general population. Several factors are known to predispose older persons to this excess risk. The first, and perhaps strongest factor is multiple drug use. Perhaps the first approach to preventing adverse drug reactions is to limit the number of drugs. This would not only reduce the chances of side effects occurring, but also reduce the possibility of drug interactions.[66]

Polypharmacy ... The incidence of polypharmacy or multiple medication use in the elderly is substantial.[34,36] One of the major associated problems is adverse drug reactions.[70] Williamson and Chopin found an increasing prevalence of ADRs as the number of prescribed drugs increased, occurring in 10.8% of those taking one drug and 27.0% of those taking six.[71] Another study of ambulatory elderly with dementia also found an increased incidence at ADR's with an increased number of medications.[72]

A number of factors contribute to the problem of polypharmacy.[73] Patients who use multiple physicians and pharmacies run the risk of receiving drugs that are therapeutic duplicates and drugs that interact since the health care professionals they see may not be completely informed about other prescriptions. In addition, there is a greater risk of medication errors and/or noncompliance due to polypharmacy.[74]

Pharmacokinetic and Pharmacodynamic Changes ... As previously mentioned, there are a number of possibly age-related physiological changes that may effect the pharmacokinetics of drugs in the elderly. There is a possibility of adverse drug reactions occurring when total body clearance of drugs is reduced either due to decreased hepatic metabolism or renal excretion. This risk is increased because the higher resulting plasma concentration should correlate with higher concentrations at the receptor site with an accompanying chance of enhanced pharmacological effects. In addition, regardless of pharmacokinetic changes, the elderly may experience enhanced pharmacodynamic response to drugs.

Often, however, it is difficult to determine which mechanisms, if not both, simultaneously contribute to adverse drug reactions. For example, a study from the Boston Collaborative Group has shown that at high doses of flurazepam (= or > 30mg) 39% of patients 70 years of age or older, experienced adverse drug reactions.[68] This compared to an incidence of 2% in the same group taking 15mg/day of flurazepam. A later study of flurazepam kinetics found a prolongation of its half-life in elderly men.[75] However, there are several studies of similar benzodiazepines in which the elderly had greater central nervous system sensitivity than younger subjects despite having the same drug plasma concentrations.[76,77]

Drug Interactions ... Traditionally, the term drug interaction (DI) has been defined as the effect -- either favorable or unfavorable -- that the administration of one drug has on another drug. Only a few studies examining DI's in the elderly have been reported. In a study of 573 hospitalized elderly, 2.16% of prescriptions written during their hospitalization produced potential drug interactions.[78] The investigators classified 78.2% of those interactions as avoidable or probably avoidable. Drug interactions in a 1975 nursing home survey of 562 patients were found in 5.8% of medication orders.[79] Another study of 132 nursing homes and 11,173 patients found that 2.7% of patients had clinically significant drug interactions occurring.[80] The occurrence of drug interactions among 1,094 ambulatory elderly was found to be much greater than that in the institutional populations (15%).[81]

It is not clear what proportion of potential drug-drug interactions are actually of clinical significance. For example, in one study 80% of the patients only required close patient monitoring as opposed to dosage reduction or drug discontinuance.[80] Still, the elderly are at an apparently increased risk for drug interactions as a consequence of the prevalence of polypharmacy. Also, in individual elderly patients who have altered homeostatic mechanisms and limited functional reserves, drug interactions may cause significant morbidity.

There are two major types of drug-drug interactions: pharmacokinetic and pharmacodynamic. Pharmacokinetic drug interactions occur when one drug alters the absorption, distribution, metabolism, or elimination of another drug. Interactions with the greatest potential for adverse drug reactions are those involving a decrease in the total body clearance of drugs with a narrow therapeutic index. For example, cimetidine has been shown to decrease the clearance of antipyrine, a marker of oxidative liver metabolism.[82] Pharmacodynamic drug interactions occur when one drug either enhances or diminishes the pharmacological effect of the other drug. This usually involves an interaction at the site of action or the receptor level. Of particular importance in the elderly is the cumulative effect of drugs with different desired pharmacological effects but similar side effects. For example, alcohol is reported to significantly contribute to sedation experienced by patients taking drugs with central nervous system depression side effects such as antihypertensives of psychotropics.[83]

Drug interactions in an even broader context include their adverse interactions with disease processes, foods, or laboratory tests. Drug-disease interactions, although less common than drug-drug interactions, have a greater potential to produce clinically meaningful adverse effects.[79,81] Information about drug-food (drug-nutrient) interactions is increasing.[84] It is well known that some foods can alter the pharmacokinetics of drugs, but drugs can alter appetite and/or cause vitamin deficiencies as well.[84] An area of current research interest is the effect of nutritional deficiencies on hepatic function and drug metabolism.[85] Drug-lab interactions (drug induced alterations of laboratory values) require careful evaluation and interpretation. They may indicate drug-induced illness or statistically significant, but clinically insignificant changes in laboratory test values. With growing interest in self-care and the in-vitro home diagnostic market, it will be imperative that patients and health care professionals understand that drugs may interfere with test results.[86]

3. BIO-EQUIVALENCE AND GENERICS. Generic prescription products provide a potential cost savings for the elderly. However, this potential has not been fully realized. The older consumer has shown reluctance to request generics in spite of potential savings. Reasons include perceived safety, efficacy, and financial risks; preference for the known product; and uncertainty about quality.[87,88,89]

There is a considerable debate about the use of generic drugs.[90] Since the passage of the 1984 Drug Price Competition and Patient Term Restoration Act, there has been an increasing number of generic products approved by the FDA.[91] One potential benefit of generics is that they are usually less expensive than brand name drugs. This should translate to cost savings for elderly patients. A recent study, however, questioned the cost savings of generic drugs and found wide variations in the prices of generic and brand name drugs.[92] Some have used this data to conclude that "it is not unusual for a generic drug to cost more than a brand name drug."[93] It is important to point out that in this study the consumer usually paid less for generics. Also, the study was conducted during 1984 before the new law took full effect.

Concerns have also been raised about the efficacy of generic drugs in the elderly.[94,95] This may stem from the fact that prior to approval for marketing, the studies required to prove bioequivalence are single-dose bioavailability studies of only 20-30 young health male volunteers. In addition, statistical variations as great as a 30% difference in generic vs. brand name drugs are acceptable.[90] Although the question of how this information specifically relates to the elderly patient is not fully answered, it is important to note that since 1984 there has not been a documented report to the FDA of a serious problem with a generic product.[96]

BEHAVIORAL ISSUES / The elderly appear to be particularly vulnerable to their own attitudes toward taking medications and the attitudes of others providing care. Straus has reviewed the complexity of behavioral issues as a risk factor in geriatric drug use.[97] Issues of compliance and attitudes provide a useful background to the larger topic.

1. COMPLIANCE. Assuming that a certain prescribed or OTC medication is beneficial, medication compliance or adherence is imperative to achieve therapeutic success. Numerous studies have shown, however, that whenever self administration or discretionary action is involved, patients frequently fail to take their medication as prescribed.[98,99,100,101] Patient noncompliance to prescribed therapies can have serious consequences. First and foremost, noncompliance can neutralize any therapeutic benefits of medical care rendered. Second, medication errors and/or medication noncompliance can lead to adverse drug reactions. Third, it has been associated with higher rates of hospitalization, longer length of stay in the hospital, and increased ambulatory visits, resulting in additional and unnecessary diagnostic and treatment procedures that generate avoidable costs.[102,103,104]

There is considerable controversy whether the elderly are less compliant with medications than younger patients. Two studies among noninstitutionalized elderly conducted 24 years apart reported an approximately similar medication error rate (59% and 50%).[74,98] Also, when the elderly were compared to a younger population, compliance rates were again similar.[105,106] Indeed, noncompliance seems to be associated with an increasing number of drugs rather than an increasing number of years.[107] An added dimension compounding the problem at the clinical level is the fact that physicians tend to overestimate their patients' compliance with prescribed regimens.[108]

Patient factors implicated as contributors to noncompliance include behavioral, social, and personal considerations. There is difficulty attributing health related behaviors, such as compliance, to the aging process. Not only are there methodological constraints (prevalence data vs. life course incidence data), but health behavior is also related to the social circumstances and historical context of an individual's life.[109] Nonetheless, an individual's perception and response to illness clearly influence his/her drug-taking behavior.[110] Eraker et al. have proposed a model for patient behavior which combines components Becker's earlier Health Belief Model and patient preferences.[111] This thoughtful approach to the issues of compliance contends that the matter is one of shared responsibility between physician and patient. One premise of this model is that the physician's responsibility is inversely related to the degree of patient participation; thus, the less responsible the patient, the more so must be the physician.

Social isolation has been found to play a significant roll in noncompliance.[112] A large proportion of older Americans live alone, increasing their likelihood of having compliance problems. In addition, one-third of the approximately 20 million Americans classified as illiterate are 60 years of age and older[113] compounding the potential risk of misunderstandings or lack of knowledge about therapy.[114] Other patient factors include personal impairments such as difficulties with vision or memory or learning disabilities,[115,116] and physical limitations imposed by arthritis or other handicaps.[117] There is also evidence that some nonadherence in the elderly may be intentional[118] and perhaps represent intelligent noncompliance.[119] In addition, it appears that economic issues play a role in noncompliance among older persons. A 1986 AARP telephone survey of a population (sample size not available) 45 years and older found 13% of those deciding against having prescription filled doing so because of cost.[91]

3. **ATTITUDES.** Provider attitudes may place the elderly, especially the poor elderly, at an increased for substandard medical care.[120] In spite of more prescriptions per office visit for older patients,[8] office practice encounter time with older patients is apparently less than with younger patients.[121] Perhaps this results from a perpetuation of the agism myths which Surgeon General Koop sees as self-fulfilling prophecies.[122] Wetle has suggested that this may partially be attributed to misapplication of population-based data.[123] Applying average life expectancy data in making individual management decisions deprives the patient of credit for surviving to the moment of care; the more appropriate issue is the life expectancy beyond this encounter for the individual patient.

ECONOMIC ISSUES / More than 30% of the national health care budget is spent on care for older Americans.[3] Nevertheless, this does not come close to covering the full expense of health needs of the elderly. Beyond this, out-of-pocket payments and third-party payors account for additional health expenses.

1. **PERSONAL EXPENSES.** A high rate of use and the large out-of-pocket expenditure for drugs place economic concerns on a par with safety and efficacy as important medication issues to be faced by the elderly. There are more elderly, and more of them are using more expensive drugs. Prescription prices in the U.S. rose 56% from January 1981 to June 1985; this far out-paced the Consumer Price Index which grew 23% over the same period. National telephone surveys by AARP in 1985 and 1986 found 62% of the elderly to be taking prescription drugs on a regular basis, with just less than half (45%) receiving some assistance from insurance or other health coverage. Among those without assistance the number of older patients paying more than $40 each month increased from 24% to 34%.[91] The extent of poverty (12.4% in 1986) among older Americans has remained at or near current levels for several years.[124]

Currently, Medicare coverage for outpatient medications moving through legal hurdles and final implementation. Overall, the potential cost of drugs under Medicare depends on the number of participants, the number of units per participant, and the unit cost of medications prescribed. Each factor is rising. In 1967 less than 78% of Medicare beneficiaries were taking medications; by 1980 the proportion had grown to more than 80%. Over that same period the average number of prescriptions per beneficiary grew from 10.4 to 12.1 annually. Because prescription size (doses dispensed) has increased over that same period the growth curves cannot be compared, but the average prescription cost more than doubled going from $4.00 in 1967 to $8.05 in 1980; in 1984 the cost for Medicare beneficiaries was over $10.00 per prescription.[125]

Although there are some state pharmaceutical assistance programs,[126] Medicare does not pay for outpatient drugs at this time. They will, however, reimburse for drugs administered as part of an office visit, with the notable omission of influenza vaccination. Perhaps Medicare use of health maintenance organizations in the future may change this policy.[127] For elderly patients that fall below a certain income level, Medicaid coverage of medications is available. In 1986 an estimated 6.6 percent of the elderly were covered by Medicaid insurance.[128] A recent study analyzing different Medicaid cost-saving programs found that the elderly had less access to "essential" medications [as determined by an expert panel (e.g., insulin, thiazides, furosemide, digoxin)].[129] The use of generic drugs may be an approach for patients and third parties to reduce medication costs.

New factors in understanding the cost of prescriptions are encountered each year. An estimated 5% of physicians are now dispensing drugs they prescribe, with nearly one-third of office-based MD's expected to do so "within a few years."[130] It's probably too early to appreciate the full impact of physician dispensing on drug costs for the elderly, but analysis by the Pennsylvania Department of Aging in the fourth quarter of 1986 found that elderly patients paid nearly $2.00 more per prescription when doctors dispensed the medication. The report did not indicate whether wholesale cost or quantity dispensed had been controlled in the analysis.[131]

2. **PAYMENT AND REIMBURSEMENT.** A major activity now under legislative consideration and enactment is the reimbursement of outpatient drugs for Medicare beneficiaries. Regardless of the exact outcome of this activity by the current Congress, this area will be of major interest for health economists and government officials for years to come. Although the primary concern of Medicare beneficiaries is the substantial out-of-pocket costs associated with prescription drugs, the primary concern of government officials is the cost of such a provision.[132] Given the finite dollars that Congress envisions for this benefit and the demographics of this benefit as a dramatic growth area, further refinement and adjustment will almost certainly occur with the introduction of the benefit.

At the request of the Health Subcommittee of the Senate Finance Committee, the Office of Technology Assessment (OTA) has submitted an examination cost containment strategies and possible approaches appropriate to drug coverage under Medicare.[133] Some (but not all) of the specialized cost-containment mechanisms offered for further exploration by OTA include various forms of price setting, provider and patient incentive programs, beneficiary cost-sharing programs, Federal grants to state pharmaceutical assistance programs, and developing a federal restrictive formulary.

Options for defining drug coverage under Medicare are limited. Comprehensive coverage, acknowledged by OTA to be the most expensive, might include all prescription drugs or all drugs prescribed for documented chronic diseases. Over-the-counter medications could be a component of this program. A limited coverage approach, on the other hand, could finance only selected therapeutic categories or targeted sub-populations (e.g., poor elderly or nursing home residents). Some options for specifying drug groups for coverage included determination of "life-sustaining" drugs by medical consensus, identifying drugs likely to prevent hospitalization with its associated costs, and approval only for drugs (or drug products) for which the manufacturer can demonstrate specific evidence of efficacy and safety when used by elderly patients. A third option available under Medicare is "phased-in" implementation drug coverage. This approach could allow for administrative consideration of changes in clinical practice standards, and benefit from accumulated program experience.[126]

HEALTH POLICY AND HEALTH SERVICE ISSUES / The delivery of health services and the implementation of health policy are indicators of society's expectations for health promotion. The drug component of a larger strategy is reflected in these selected examples.

1. **MEDICAID.** Although only 6.6% of the elderly were covered by Medicaid insurance in 1986, these were by definition among the least able to afford out-of-pocket health expenses.[128] Efforts to reduce costs and focus benefits under Medicaid have been a dominating health policy issue at the state level for several years. An analysis of the effects of a $1.00 copayment compared to a monthly limitation of 3 prescriptions found Medicaid's monthly savings under the two systems to be comparable.[129] However, the proportion of "essential" medications [see pg. E-10] obtained by recipients was greater under the copayment arrangement.

One approach has been the adoption of a generic formulary for Medicaid recipients by Alabama. Under that State's provisions, reimbursement for brand name drugs will not be made when generic equivalents are available. In another tack coverage of most anti-anxiety drugs was discontinued by Kansas; while coverage of psychotherapeutic drugs has been added by Arizona.[131]

Recently three states (Florida, Iowa, and North Carolina) adopted Medicaid service programs that are preventive in nature, but none of the three were directed at drugs or targeted the elderly. In 1985 Michigan adopted a therapeutic drug utilization program to identify Medicaid recipients at risk for drug induced illness.[132] In view of the higher rate of ADRs among the elderly, successes in this program ought to have greatest benefit for older recipients of Medicaid.

In view of the the increased general use of medications[28,30,133] (and psychotropic drugs in particular[28]), preadmission screening of applicants for nursing homes may shield some from overmedication while perhaps leading to more appropriate therapy for those admitted. Minnesota recently adopted a nursing home applicant screening program, and Massachusetts was considering the same in mid-1985.[133]

2. **MEDICARE.** An average 17% annual increase in Medicare expenditures between 1967 and 1983 prompted the shift to a prospective payment system based on diagnostic related groups (DRG's). This change in the reimbursement system was accompanied by increased rates of hospitalization for elderly Medicaid nursing home residents in Wisconsin.[134] Higher drug usage is usually associated with hospitalization; whether this occurred in this population is not known.

In spite of changes since 1983 Medicare costs continue to rise; and rising health care costs have financial impact on the elderly. In dealing with the issue the 100th Congress seems to favor an approach which will limit out-of-pocket health expenses to $2000 annually.[135] Proposals to expand Part B to include outpatient prescription coverage received wider support in 1987 than in previous years. Under consideration is a requirement that participating pharmacies would consent to offer medication counseling to all eligible program participants.

Prescription drug assistance under Medicare could include policy features designed to improve overall drug therapy. The OTA background paper on options for drug coverage by the Medicare Program included several policy features that might accomplish this end.[136] Among the options outlined were concepts of periodic professional review of drug regimens, limiting the number of prescriptions that can be funded, requiring a single dispensing pharmacy site, rewarding safety and toxicity studies targeted at elderly patients, and providing incentives for user-friendly packaging and labeling as well as patient education services.

3. **HEALTH MAINTENANCE ORGANIZATIONS.** Medicare recipients have been able to join an HMO since April 1985. During the two years following enactment of the legislation allowing this choice, slightly more than 900,000 (5.5%) of the eligible Medicare recipients had done so.[137] However, serious questions have been raised about the long term feasibility of a prepaid capitation system of providing health services for the elderly.[136,137] In some instances the actuarial basis for capitation payments does not reflect the population served; also, if treatments are influenced by financial self-interests the patient may suffer. In addition, a few early providers have allegedly devised enrollment campaigns which made access to enrollment sites difficult for frail or handicaped elderly. It is clearly in the interest of HMOs to promote health and prevent disease among their members; whether medications become an important facet of their strategy remains to be seen. There is some evidence that annual prescriptions per person is approximately unchanged in older subscribers but declines among younger subscribers following enrollment in prepaid health plans.[138]

4. **PHARMACY SERVICES.** Interest in mail-order prescription services has increased in recent years. Although its advantages and disadvantages have been debated in hearings and editorials, rigorous evaluation of the risks and benefits is lacking. Costs, counseling, error rates, convenience and access are the usual issues addressed. Proponents cite advantages that include savings due to an economy of scale, better ability to monitor therapy because of less "switching" between pharmacies, and convenience for less mobile patients.[139] Detractors claim higher error rates, less personal counseling,[140] and even higher costs. In 1985 an Arizona based study reported that a 4% savings in unit costs was offset by a 9% higher utilization by mail-order users.[141] It reported that changes in therapy for older users brought about more frequent ordering and increased wastage.

Labeling and packaging of prescriptions for older patients ought to take into account the possibility of visual impairments and confusion about products of similar size and color.[142] Many pharmacists use special services and "senior discounts" to attract the older patients. If such programs succeed in establishing client loyalty, the opportunity for regular counseling and ADR monitoring should benefit the older patient.

"Brown Bag" projects are programs in which elderly are encouraged to bring medications to a convenient location for review and counseling. Their focus is the ambulatory older population, and their purpose is to detect potential medication problems and correct those that need attention. One program has reported approximately 88% of participants need reinforcement, clarification, education, or health provider follow-up.[143]

5. FRAUD. The elderly seem to be less suspicious of medications that do not produce their promoted or expected results.[144] Among 172 older respondents (age 60 or older) to a 1984 survey, one-half reported purchasing a health product that did not work and just over one-half of those (53%) suspected it to be quack medicine. While appropriate cautions regarding interpretation were stated, the authors pointed out that the elderly are particularly vulnerable to fraud and the consequences of quackery because they are more likely to suffer from conditions for which many quack medications are promoted.

6. ADVERTISING. The claims that OTC as well as prescription drugs portray, either directly or indirectly, to the elderly are an area of continuing concern. Surveillance of the prescription drug claims relating to the elderly that are made directly to consumers or through health practitioners, will continue to share an area of high interest and surveillance by FDA.

E. Developing Technologies. New technologies in information management, drug products, and health service delivery bode well for improvements in drug therapy for the elderly. As computerized expert diagnostic systems become more user-friendly, the power of knowledge previously available only through years of experience should make extensive information available to all that care for elderly patients.[145] Public awareness of the special needs of older citizens has served to stimulate the application of new technologies in areas which benefit the elderly.

In the future, advances in technology are expected to result in the development of new dosage forms and new drug entities that will be more convenient for older patients as well as more specific and efficacious in their pharmacologic effects.[146,147] A number of novel drug delivery systems are currently being developed.[148] For example, transdermal delivery systems can extend a drug's duration of effect, and therefore should assist in improving compliance. Biotechnology advances are also expected to result in the development of numerous new therapeutic entities.[147,148] A number of pharmaceutical firms are currently working to develop new drugs that might reverse congnitive losses in Alzheimer patients.[149]

Geriatric assessment units have been referred to as examples of "new technologies" in health services, and have grown in number and scope since 1979.[150] A 1985 survey of 104 units found that nearly half had begun operation during the previous two years, and two-thirds of the others increased their capacity during that time. Most (approx. 60%) are outpatient units, and 27% of those reported "improvement in drug regimens" to be either their 1st or 2nd most important effect.

F. Successful Interventions and Programs. Drug related problems in the elderly do not usually occur in isolation. The several successful interventions reviewed here gave emphasis to a particular outcome (e.g., compliance, polypharmacy, adverse drug reactions, cost savings), but in most instances the intervention required multidisciplinary effort and cooperation, and effected more than one area of need.

COMPLIANCE / The success of drug-related health promotion patient interventions depends on relevance, individualization, feedback, reinforcement, and facilitation.[151] Ten strategies for reducing drug errors in the elderly were reviewed by Green et al. in 1986.[152] These investigators found facilitation to be the most common technique, with no more than half incorporating relevancy or individualizing intervention, and even fewer using feedback or reinforcement. They concluded that interventions combining interpersonal communication methods, visual materials and memory-aids had been shown to be effective means of reducing drug errors as well as related clinical symptoms in the elderly. Several of these studies compared the effectiveness of different strategies on medication compliance and errors. MacDonald, et al., found no significant difference between medication counseling and counseling with a medication calendar. Both strategies significantly improved compliance in comparison to controls.[153] Color-coded weekly medication packaging significantly reduced medication errors when compared to color-coded conventionally dispensed medications, medication counseling, and no intervention.[154] Another study compared verbal medication counseling alone and in combination with either written information, a medication calendar, or a seven day medication package.[155] Attitudes, knowledge, and compliance in an elderly ambulatory population were assessed. Drug knowledge was most favorable effected by verbal instruction alone or combined with a medication calendar. In contrast, patient reported compliance was improved only by the combined intervention of verbal medication counseling and use of a seven day medication package. In general, patients felt the interventions were useful with the notable exception of the medication calendar.[155]

EDUCATION FOR PRESCRIBING / There is some evidence that physician peer education can have positive impact on prescribing in general. Studies by Ray and Schaffner have shown that the prescribing of antibiotics and diazepam improves after receiving education visits from a physician.[156,157,158] Also, pharmacist provided drug information can favorably impact on the prescribing of specific drugs or therapeutic classes of drugs.[159,160,161] Avorn found improvement in the prescribing of cerebral and peripheral vasodilators, oral cephalosporins and propoxyphene after education visits by a clinical pharmacist. The program, involving 400 physicians, resulted in a 14% reduction in utilization.[159] Hanlon, et al., found the prescribing of the above mentioned medications and the number of medications prescribed per patient to be lower than national prescribing data in a family medicine residency program with an active clinical pharmacy program.[160] Finally, a controlled study showed that global prescribing practices were favorably impacted by continuing education provided by clinical pharmacists and pharmacologists.[161]

ADR REDUCTION and SAVINGS / Interventions by clinical pharmacists as consultants in long-term care facilities (LTCF's) have been documented as being effective. One study of feedback from the LTCF clinical pharmacist consultant reduced the incidence of medication errors, the number of inappropriate or unnecessary drugs, and the incidence of adverse drug reactions, thereby reducing medication and hospitalization costs.[153] In a long-term study evaluating the initiation, termination, and reinstitution of a consultant clinical pharmacist, it was found that there was lower drug-use, admission, discharge, and death rates during the time the consultant was with the facility.[162] A recent paper examining the cost-benefit ratio of pharmacist-conducted drug-regimen review in LTCF's estimated a net savings of $220 million nationwide.[163]

Another study monitored adverse reactions in 2,771 randomly chosen hospitalized patients during 1969-1976. Medications as well as indications for starting and stopping therapy were tabulated, and records for the 1969-72 period were compared with those for the 1973-76 period. An active surveillance and ADR reporting program during the second period resulted in a 61% reduction in the number of patients affected by reactions to drug therapy; with the greatest reductions in the two age bands over 70 years of age (69% and 89%).[164]

A novel study evaluating the pharmacist as a prescriber of drugs to previously diagnosed LTCF patients, found them to be more effective than physicians in terms of number of drugs prescribed, lower number of deaths, and increased number of patients discharged to lower levels of care.[165] The significance of this study may not be the role of the pharmacist as an independent mid-level practitioner but extrapolating this information to include the pharmacist as an integral part of a multidisciplinary team.

MULTIDISCIPLINARY COOPERATION / Nursing initiative at one teaching nursing home has targeted reduction in cathartic drug use as a priority.[166] In nursing homes conflicting schedules limit opportunities for personal contact and direct dialogue among professionals. Although drug regimen reviews conducted by nursing personnel in Iowa intermediate care facilities have identified a variety of problems, widely variable physician responsiveness to reports and recommendations has been reported.[167] In Georgia Longe et al. found that written recommendations of consultant pharmacists in skilled nursing facilities were usually effective, with 72% of drug-dosage recommendations and 80% of laboratory test recommendations being accepted.[168] In North Carolina an interdisciplinary team review approach to drug therapy recommendations resulted in a reduction in the number of medications at one long-term care facility.[169]

V. Priorities and Recommended Programs to Address Areas of Concern

THE AGING PROCESS and DRUG DEVELOPMENT / Basic research into the aging process and the diseases of aging is needed. Distinction between aging processes and disease processes is not possible in many instances.[170] Investigation into the physiology of aging will contribute to needed understanding of pharmacodynamic changes and guide drug development specifically beneficial to older patients. Health promotion and disease prevention initiatives should benefit from this basic research and, perhaps lead to the development of products that will enhance the quality of life in later years.

DRUG TESTING / In the past, there have been few carefully carried out geriatric clinical drug trials that investigated the pharmacokinetics and pharmacodynamics of drugs in older patient samples.[171] However, in recent years there has been a steady increase in information about these areas of interest.[172] FDA labeling guidelines were revised in 1979. These guidelines directed that prescription drug labeling feature special age group indications or precautions.[173] It is now common for FDA new drug applications to include analyses relating age with drug responses.[174] Evidently Phase III clinical trials are now less likely to have excluded subjects on the basis of advanced age. At FDA, Dr. Temple expects to have a formal drug testing proposal in place in 1987.[174] Although there are some disagreements about the specifics of the proposal,[175] a number of professional groups are encouraged by the FDA's requiring the inclusion of formal testing of new drugs in the elderly and improved labeling of such information. Once a drug testing regulation is approved, the clear need will be for more studies of currently marketed drugs (Phase IV) in older patients.

Clinical drug trials in which subjects are stratified on age and factors known to alter drug disposition are controlled. These studies are needed in order to identify agents for which pharmacokinetic changes are truly age-dependent. This approach to testing would provide elderly patients with maximum benefit at minimum risk and allow companies developing new drugs to inform prescribers of true factors effecting dose.

POST-MARKETING DRUG SURVEILLANCE / The field of pharmacoepidemiology, or the study of drug use and drug effects using specific epidemiological methods has emerged in recent years.[176] Interest in post-marketing surveillance (PMS) of drugs and their effects is evident in several sectors, including the government, the pharmaceutical industry, and third party payors.[177] Investigations carried out once a new product has been marketed (Phase IV studies) can include careful assessment of spontaneous reports, additional clinical trials, cohort monitoring, and case control studies.[178] Two primary objectives of PMS are an assessment of efficacy and toxicity under conditions of actual clinical use, and an evaluation of the relative impact on approved indications.[179]

There are a number of data-bases which investigators utilize to study drug use, some of which were previously mentioned in this paper. Recently, there has been great interest regarding the effects of non-steroidal antiinflammatory drug since they are so widely used in the elderly; several studies utilizing the Medicaid Drug Event (Compass) Data Project,[180] The Boston Collaborative Drug Surveillance Program,[181] The American Rheumatism Association Medical Information System (Aramis),[182] and the FDA data-base have been published.[183]

In view of the evidence that older patients are at higher risk of adverse drug reactions and may exhibit atypical response to therapy, PMS in populations 65 years of age and older seems particularly advisable. Presently there are limitations due to the inherent nature of the data-bases themselves,[184] and the lack of a comprehensive national system.[185] There are, however, encouraging signs that the field of pharmacoepidemiology will continue to emerge and play an important role in knowledge of drugs and the elderly.[186,187]

LACK OF TRAINED PROFESSIONALS / Specialized knowledge of clinically important pharmacokinetic and pharmacodynamic changes that often accompany the aging process are needed for prescribing for the elderly.[188,189] It has been persuasively argued that many problems associated with prescribing can be avoided,[69,78] and yet about half the physicians delivering care in geriatric assessment units have no special training in care of the elderly.[190] Specialty training programs in gerontology and geriatrics offer one approach to imparting the specialized knowledge needed to avoid such problems. Unfortunately projections of population growth, particularly in the numbers of frail "old-old", strongly support the contention that requirements for geriatric specialists over the next decade will not be met.[190,191,192,193] At present there are 66 geriatric medicine programs and 27 geropsychiatry programs in the U.S.[193] A new fellowship program to train 4-6 physicians in geriatric clinical pharmacology will begin in 1988.[194] At a broader and more basic level, medical schools are providing only minimal training of geriatrics.[191]

Federal law mandates that a pharmacist review the drug regimens of all LTCF patients. This regulation has resulted in decreased exposure to unnecessary drugs and an associated decline in the cost of drugs in nursing homes. In addition adverse drug reactions and subsequent hospitalizations have also declined.[195] Although this role is established, there are only three accredited pharmacy residencies in geriatrics, and ten funded geriatric pharmacy fellowships in the U.S.[195,196] A 1985 survey of U.S. Schools of Pharmacy found that 40 schools planned to incorporate an AACP developed text on geriatrics in their coursework.[197] At least 10 schools indicated plans to offer geriatrics courses not previously available. The Geriatric Education Centers (GEC) Program has also stimulated expanded training in geriatric drug therapy.[198]

Whether responsibility for drug therapy management of elderly patients should be a shared or independent exercised, there is agreement that neither medicine[199] nor pharmacy[196,198,200] will provide an adequate number of specialized practitioners in the near future. Interdisciplinary training programs designed to enhance cooperative relationships between physicians, pharmacists and nurse-specialists should shorten the period during which the elderly can anticipate the shortage of geriatric drug specialists.

REIMBURSEMENT FOR SERVICES / Among issues usually associated with Medicare reimbursement, medication for the elderly is not typically considered. However, the opportunity (or risk) to receive medications begins with access to the prescriber and so reimbursement policy that effects access will probably effect drug utilization patterns as well. The American College of Physicians has recently published a position paper on alternative payment approaches for Medicare in which it suggests that inequities in the present reimbursement system "induce physicians to provide technologic and procedural services as opposed to cognitive and interpersonal services such as history taking, preventive health care, or patient education and counseling."[201]

FINANCING / An immediate assessment of the probable financial consequences of ambulatory drug coverage under Medicare is needed. The potential impact of such coverage on prescribing, pharmacy services, and self-care practices has not been studied.[136]

VI. Summary

Drug therapy represents an important approach to promoting health in the elderly. Rational and judicious use of medications can enhance the quality of life for older patients with chronic diseases. Wide variations in body compositon and organ system function exist among older persons. Consequently the clinical management of individual elderly patients demands caution and an appreciation of the possible variations in drug response. Respect for these nuances in drug response are essential to rational prescribing for the elderly.

It appears that drug usage in the elderly is considerable in terms of medications taken and associated expenses. There are also patterns of medication use which, while easily understood, suggest the need for greater prescribing forethought in subsets of the 65 and older population. For instance, increased prescribing for and general use of medication among older women; an increase in the number of medications with advancing age continues into the ninth decade of life; and more medications ordered in settings where higher levels of care is provided.

Changes in pharmacokinetics and pharmacodynamics can contribute to adverse drug reactions in the elderly. Polypharmacy (a major reason for drug interactions) and non-compliance (particularly excessive dosing) can also contribute to the incidence of ADRs. It is often difficult to predict the specific cause making advisable the use of lower initial doses with careful dose escalation titrated to therapeutic response.

As new drugs designed specifically for geriatric needs are developed, as additional training programs are funded, as new technology raises health costs in general, and as the number of elderly over 75 increases, the questions of "Who pays?" and "How much?" take on even more challenging dimensions. The issues to be faced in providing affordable, safe, and effective medications for older people in the U.S. are plentiful today, but will surely be even more numerous beyond the year 2000. 1988 is not too soon to begin to address them.

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Item 2

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DRUGS AND THE ELDERLY

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As the US population grows older, there is an increasing need to understand how drugs work in the elderly. Bodily accommodations to aging, but more importantly, disease states that occur in the elderly, must be studied to ascertain how drugs affect health and well-being. Assuring proper testing and surveillance of drug use, as well as effective clinical research in the elderly, are important means to this end.

Key Words: Aging; Drugs; Disease states; Drug studies

"FOR THE ELDERLY, this may be the age of safe surgery and dangerous medicine."[1] Since this statement was first made in 1972, little has changed in the field of geriatric medicine except that the importance and urgency of our imperative has become clearer.

I believe we all recognize now that we are in the midst of a worldwide demographic revolution. Europe and North America have the highest percentages of people over the age of 60, but other regions of the world are experiencing very rapid increases of their populations of elderly. In the United States, between now and the year 2020 (which is within the expected lifetime of almost everyone at this symposium), the number of persons age 65 and older will double, from 27 million to more than 52 million; they will, by then, represent 20% of the population.

The even more rapid increase of the oldest old, those 85 years of age and older, presents a more immediate challenge. Again, in the United States, in the next 15 years, the number of those in this oldest old group will double, from 2.6 million to about 5.5 million. Based on current practices, this will mean a 30% to 50% increase in acute hospital bed days and a 50% increase in the number of nursing home bed days by the year 2000, unless we improve our preventive treatment and rehabilitative care. In addition, we must develop more effective and acceptable arrangements for maintaining frail older people in their homes, which they generally prefer.

Although many more people are living into their very late years in good health and vigor, we all know that the prevalence of chronic diseases and conditions increases with aging. According to National Center for Health Statistics' data on the prevalence of the most common chronic conditions, almost half of all older people report some form of arthritis, mostly osteoarthritis. Such chronic conditions result in progressive loss of ability to carry on daily functions and maintain fully independent lives. The most recent data from the National Center for Health Statistics indicate that approximately 20% of persons aged 75 and older, and 40% of those aged 85 and older, require some help from another person for one or more aspects of daily living.

In the face of these challenges, we need to deal with a number of issues related to the use of drugs in older people. We need to understand how drugs work in this population and clearly distinguish between aging itself and the effects of diseases.

The previous view, that aging is inevitably associated with a progressive decline in the function of virtually all body organs, is being challenged today. In recent studies, more sensitive approaches have been used to identify older persons with various diseases, and those free of disease have shown remarkable organ function into their seventies and eighties. One of the best examples involves cardiac function. In studies recently reported by Rodeheffer et al,[2] ostensibly healthy, normal volunteers in the National Institute on Aging Baltimore Longitudinal Study of Aging were first screened for even subtle degrees of heart disease using radioactive thallium scans of the heart during exercise tolerance tests. Approximately 50% of the subjects in their seventies and eighties had evidence of areas of poor perfusion of the heart muscle, indicating some degree of coronary artery disease. When the remaining 50% with normal tests were studied for cardiac output during standard stress tolerance tests, participants in their seventies and eighties had the same range of maximum cardiac output as the younger participants, with no evidence of an age-related downward trend. There were changes with age in the way the heart responded to exercise, namely, less increases in rate but greater increase in stroke volume. However, the study clearly showed that overall cardiac output can be maintained into the very late years if coronary artery disease does not develop.

The brain is another organ that, in the absence of disease, functions effectively and efficiently into the late years. Positron emission tomography, using radioactively labeled 2-deoxyglucose to measure brain metabolism, showed no significant age-related change from age 20 to age 80 in a group of healthy men. Longitudinal studies of mental function have shown only minimal changes in intelligence in individuals as they age.[3]

Studies of the aging kidney are of particular importance in relation to pharmacokinetics. Early studies indicated a significant downward trend in glomerular filtration rate and renal plasma flow with aging in normal individuals. However, most recent studies of healthy individuals conducted in the Baltimore Longitudinal Study population gave quite different results. In approximately 30% of the participants, there was no change in glomerular filtration rate with aging; in 5% there was an actual increase in glomerular filtration rate with aging; in the remaining 65%, there was a moderate, sustained decline with aging.[4] Thus, one cannot say that aging, in the absence of disease, is invariably associated with a decline in renal function. More importantly, we must be aware of the variability in renal function in older individuals and the need to assess the renal function of each older patient before prescribing medication for that patient.

There are, at the same time, well-documented changes in cell characteristics with aging that have implications for pharmacodynamics. A diminished responsiveness of cardiac muscle to catecholamines has been found to explain the reduced increase in heart rate with exercise.[5] There are somewhat similar changes in responsiveness of other tissues to various hormones, such as diminished responsiveness to insulin. There also are changes in the structural confirmation of intracellular enzymes. The precise mechanisms of these aging changes are the subjects of active investigations. My overall conclusion is that we need to study, at all levels of biological organization, the characteristics of aging as distinct from the effects of disease in older people.

Even more important in considering drug testing and development in the elderly is the fact that most older people suffer from several chronic diseases, and it is necessary to consider the effect of drug pharmacokinetics, pharmacodynamics, and interactions in the presence of such diseases. What, for example, will be the effects of a promising new calcium channel blocking agent for treating hypertension or angina in people aged 75 or older who also have diabetes (20% of all people over 75 years of age do have diabetes) or in people aged 80 or older who also have significant dementia (at least 20% of people over age 80 do suffer from dementia)? Or, what are the effects on Alzheimer's disease of anticholinergic agents that may have promising beneficial effects on urge incontinence?

It is also necessary and important to know about the effects of drugs on the overall functioning of older persons: Drugs may alter nutritional status by affecting appetite or taste. By suppressing central nervous system function to even a modest degree, drugs may diminish the patient's sense of well-being or produce clinical depression.

In both human and animal drug studies, it is necessary to test over the entire life span and, specifically, to make distinctions between changes in response that may occur in the maturing years and those that may or may not occur during senescence. Too often in the past, the results of studies carried out in young, immature animals (or humans) have been compared with those of studies done in late life. The differences attributed to aging may have simply represented the still maturing features of the organism. Examples can be cited in which changes in hormone or drug responsiveness continue to occur up to the age of 30 to 40 in humans and thereafter show little change into the late years; a comparison of test results of people in their twenties with people in their sixties and seventies might suggest a senescent effect, whereas comparing them with findings of people in their forties would suggest a maturational effect.

In the design and execution of drug studies in older people, it is essential that individual psychosocial characteristics of older people, including life-long patterns of response, be considered. Attention must be paid to cultural differences. The approaches to obtaining informed consent must be sensitive and thorough. The experience gained in demonstrably successful trials such as the Systolic Hypertension in the Elderly Program conducted by the National Institute on Aging and the National Heart, Lung, and Blood Institute should be drawn upon.

Experience has shown that it is advisable to present the research proposal in detail at least twice to an older person, and to include the person's closest relative(s) and/or primary care givers, unless the older person expressly requests that this not be done. Many older people are quite interested in participating in research trials, understand the social importance of such trials, and enjoy the increased attention they receive as participants.

Achieving patients' compliance with or adherence to planned therapeutic regimens is a problem often encountered in such trials. An added complicating feature in some older persons is a decline in memory. It is often advisable and necessary to involve a family member or other primary care giver to assure adherence.

The National Institute on Aging, in working to fulfill its chartered mission of research and training in the biomedical, behavioral, and social aspects of aging and the problems and diseases of old age, supports a variety of studies dealing with the basic and clinical aspects of pharmacology in older and aging people. We see our role as complementing that of the Food and Drug Administration, and look forward to continuing to work with the FDA in addressing more successfully the special needs of older people.

There is no single, simple way to characterize old age. People change continuously throughout their entire life span and the rate and extent of change are individual. More important than age per se as a variable are these individual differences as well as the presence and effects of a variety of chronic diseases and conditions. These factors provide not only the reason for drug intervention but are the complicating features which require the most careful, individualized approach to the use of drugs in older persons.

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Item 3

GERIATRIC DRUG USE–
CLINICAL & SOCIAL
PERSPECTIVES

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Chapter 8

SETTING THE AGENDA FOR GERIATRIC DRUG RESEARCH

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Part of the difficulty in setting the agenda for geriatric drug research is that much has already been said and many have called for more investigation. Another difficulty is that we are in such an early stage of addressing specific issues about the relationship of drugs to older people that much work still needs to be done. Furthermore, the commitment to research on drugs related to the elderly is still very small compared to the rapidly expanding number of older people, who are inevitably going to be using a sizeable number of drugs. Partially this is because investigators have not brought forward challenging research proposals, and partially it is due to the competition for the research dollar. Also, after talking to persons from the pharmaceutical industry, I have learned that there has been very little direct addressing of issues related to aging and drug effects. Looking at all these factors, I think we have a stake in trying to expand our commitment in this field. If there is any message, it is that we all have much farther to go to address research issues on drug use and older people. I will try to highlight a few of the areas that should be on our agenda.

DIFFERENTIATION OF AGING FROM DISEASE

First of all, as a basic starting point, we still need to learn much more about aging per se and how to differentiate aging from disease. What changes in the normal — biological or psychological — state are brought by the passage of time? Then, can we in turn relate those changes to responses to drugs? The importance of understanding age-related changes cannot be overestimated because the more we learn the more we find that most declines in bodily function that occur in the later years are due to disease and not to aging. I want to cite two examples of such new information. One recent study just completed by scientists at the National Institute on Aging's Gerontology Research

Center in Baltimore in collaboration with scientists at The Johns Hopkins Hospital shows that in people in their 70s who had no evidence of even occult coronary artery disease, their maximum cardiac output, under standard stress tests, was as good as that of 25-year-olds.[1] There was no decrement in cardiac output provided they were free of coronary artery disease as established by screening with radioactive thallium scanning to detect even slight degrees of coronary artery disease. About half of the people in their 70s showed no evidence of coronary artery disease even with this advanced type of screening. So we have to rethink our views about an age-related loss in cardiac function, as it appears that the decline so often seen is attributable to disease.

Mental functioning is another area where it has long been assumed that declines occur with age. Recent research has clearly shown that in normal people there is essentially no decline in mental functioning compared to that individuals's own intellectual status earlier in life. This was true of about 80% or more of the people followed in several careful longitudinal studies.[2] There are some slight differences in tests of elements in mental functioning between young and old but overall performance held up extremely well, and that is quite contrary to what has been the general perception of most of our society. Remember that we used to think that everybody eventually became senile; that idea has now been disproven. Today we recognize that a significant number of people suffer from Alzheimer's disease or other dementing disorders but that it is far from a universal affliction. However, most people are still carrying around the lurking suspicion that all of us will lose some mental capacities as we get older even if we don't get a true dementing disorder. The fact is that this is not necessarily true. I think that as we examine brain function with more and more refined techniques we are going to find that aging alone produces minimal changes in the brain and organ functions. That does not mean that there will be no changes in the structural characteristics of body tissues with the passage of time, even without damage from disease or injury. There are changes in connective tissue, changes in the cell membranes, and changes in the nature and extent of the receptor cells for hormones or drugs. We need more research on such changes. But first we need to start from the premise that it is essential to understand and separate out what is aging and what is disease.

A second basic premise is that, in considering the effects of drugs in older people, we have to recognize that most older people do have some chronic disease. Eighty percent or more of people over the age of 65 have at least one diagnosed chronic disease, including such common problems as hearing or visual impairments, arthritis, diabetes, and cardiovascular disease. By the time people reach their 80s, virtually all have at least one diagnosable chronic disease and most have more than one. When we discuss drugs in older people, we must take such facts into account. Consequently we need to study drugs in older people and in the known presence of multiple complex problems. Standard procedure has been to study drug response in a situation free of any compounding variables and this is simply not useful in studying the effects of drugs in older people. The effect and effectiveness of any drug in old people is going to have to be tested and interpreted in the light of a variety of potentially compounding diseases and problems. This issue will be more important as our population over the age of 85 doubles between now and the year 2000.

SPECIFIC BODY CHANGES IN RESPONSE TO DRUGS

Another area that needs consideration and further research is pharmacodynamics. We know very little about aging and changes in drug receptor responses or about what happens inside cells after the drug receptor reaction occurs. At the Gerontology Research Center in Baltimore, current studies are indicating that the regeneration of beta-adrenergic receptors is much slower in older animals compared to younger animals. We need to learn much more about this and, at least in theory, its relation to every type of drug that is commonly used with older people. It has been pointed out that, in the development of drug research, manufacturers usually concentrate on one of a family of potential chemical compounds that seems overall to have the best beneficial to adverse effect ratio for a given purpose. This is, however, usually determined in younger animals or younger people, and it might well be that some other member of a family of compounds would be much more appropriate in older people perhaps because, for example, it has less duration of effect on receptors. Thus there is a whole realm of drug cell interactions to consider in differentiating between old and young members of a species.

I want to caution here that much of the research aimed at identifying changes with aging both in animals and in people compares very young animals or people, adolescents, if you will, with old animals or people. For example, 3- to 6-month-old adolescent rats have been compared with rats aged 24 to 36 months. It appears to be inappropriate to compare such very young, still-maturing animals with very old animals, without including animals in early maturity, say 12 to 15 months of age.

The same problem occurs in humans, for example in studies of drug effects in relation to age when the comparison is of 25-year-olds with 75-year-olds. In such cases, decrements will be found and often classed as age-related effects. In fact, in some instances where this has been explored further it has been found that the apparent decrements in response occurred in early middle adult life. The big differences are seen between, say, 25- and 40-year-olds, with little change beyond that age in humans. This is an important distinction. Some effects have a linear decrement of age beyond the point of maturity, but a number of conclusions from studies have been misleading in attributing to senescence a decrement that really occurs relatively early in life. Probably the correct interpretation would be that there was a more active change during adolescence or early maturity that was actually a biologically normal part of the maturing process, but then a lower level of function becomes appropriate for the stable mature phase of that particular species. Therefore, what we labeled "senescent" wasn't actually an effect of senescence at all. This raises a methodological principle that has to be considered when talking about senescent effects in drug use or about any other physiological studies.

COMPLIANCE

There are other areas that fall outside the biological and basic pharmacological realm but are equally important in research on aging. One of them has to do with the whole question of compliance. I learned years ago in my own research how relatively poor compliance was among people with diabetes. They failed to carry out not only the proper use of drugs but also recommendations for diet, exercise, and urine testing — all the active measures a person with diabetes can take to maintain best health. In one way or another over 60% to 70% had some difficulty with compliance.[3,4] An interesting sidelight was that taking insulin was the only area where compliance was very high, even though 20% to 30% errors in dosage occurred. It seems that the actual fact of giving oneself an injection each day seemed to be enough of an event that almost all diabetics gave themselves their injections. Their compliance in taking oral antidiabetic drugs was no better than in the results of other studies of tablet taking. About 25% failed to take their antidiabetic drug at one time or another. Conceptual models are being developed and tested for their value in guiding efforts to improve compliance. Marshall Becker and colleagues, in their recent review, presented a health decision model in which the recommended elements for study were presented as well as an approach for achieving better compliance.[5] We need to develop individualized strategies in relation to the way a given person responds. I might just illustrate this again from diabetic studies where we found that patients who wanted to be told exactly what to do — about 20% of all diabetics — and who had a doctor who felt that rigid control was the proper method did very well. If such patients had a doctor who had a lackadaisical attitude about diabetes, they did not do very well. And, the reverse was true: if the doctor had a rigid view about diabetes management and the patient a lackadaisical view, again the patient did not do very well. If both doctor and patient had a more relaxed attitude about management of diabetes, then the patient did better than when there was a conflict in approach. In other words, congruence between patient and physician in approach to diabetic management was a distinct advantage. This suggests that we need to be able to define such patient and physician characteristics and adjust our management approaches accordingly.

ADMINISTRATION OF MEDICATIONS TO THE ELDERLY

We need to have more imaginative efforts to make medication administration as foolproof as possible. Some older people do suffer from forgetfulness and some have physical limitations, and special efforts to develop ways to assist such persons in taking medications would surely be of wide benefit. Consider the question of more use of the transdermal approach for administering medication. Then one can tell by looking at a patch on the arm that the patient has applied the drug and not have to think about whether the pills have or haven't been taken. We need to consider, from a pharmaceutical point of view, ways to package drugs that will minimize confusion for patients. Perhaps a highly individualized approach could be taken where a pharmacist would provide a patient with morning pills in one sealed package, and afternoon pills in another sealed package. Patients or families often have to produce such packages themselves, but I don't see why a pharmacist couldn't do such packaging. At times I have asked a pharmacist to prepare a mixture of insulin because the patient was not capable of mixing it, and that has served the patients very well. Pharmacists can help a lot of people to achieve more effective regimens. This is product development, perhaps, rather than research, but it is an area that needs attention.

There are obviously many areas in which we need much more basic drug research and development. For example, Alzheimer's disease presents a cardinal area in geriatrics where our chance to manage that disease more effectively is going to depend either on discovering a cause that we can prevent or on discovering a medication that will reduce symptoms. Alzheimer's disease presents a vast challenge for research related to aging.

Training

Finally, I want to mention the whole area of training. One of the major missions of the National Institute on Aging is to provide support for training and research and teaching in the fields of aging including use of drugs with older patients. We desperately need more people in our medical and other health profession schools to take the lead in teaching and in research in pharmacological and pharmaceutical issues in aging. The National Institute on Aging will encourage and support additional development of training in this field. The recent *Report on Training in Geriatrics and Gerontology*, prepared by the Public Health Service at the request of Congress, gives a detailed analysis of the needs for more trained professionals in these fields, and makes recommendations for meeting these needs.

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Item 4

Pharmacology and geriatric practice: A case study in technology nontransfer

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Use of medication in the elderly in contemporary medicine presents a paradox that is both fascinating and frustrating. Powerful, effective new medications are being developed, at great cost, to relieve disability and prolong life as never before. Elegant research is gaining momentum, clarifying relationships between aging and drug therapy for both established and new agents. The population in need of this therapy is burgeoning at an unprecedented rate, particularly the oldest and sickest segment of the elderly. Yet there is a growing chasm between the insights gained in the laboratory and in clinical research and the therapeutic experience of the average older patient.

Part of this problem is not unique to pharmacotherapy. It is by now well recognized that geriatrics as a whole is a discipline neglected in all phases of medical education and training, despite the central importance of this field in the practice of modern medicine. Ironically, a similar observation has long been made about pharmacotherapy itself. It is thus not surprising that pharmacotherapy in geriatrics should be a topic that is sorely underrepresented in medical training, even though prescribing medications to older patients is one of the central aspects of medical practice today and destined to become even more important in the coming decades.

The evidence of the growing gap is not hard to find. The first line of evidence comes from data on patterns of use. Sedative/hypnotics with unacceptably long durations of action or side effects are still used with surprising frequency.[1] Older antihypertensive medications with high potential for adverse effects in this population are still prescribed widely despite the advent of newer, more precise therapies. Nostrums promoted for treatment of senile dementia are commonplace despite negligible evidence of efficacy.[2] Neuroleptics are disturbingly popular as behavior-altering treatment in the aged, even in the absence of a specific indication for their use, placing patients at especially high risk for the long-term complications of tardive dyskinesia, as well as frequent concurrent adverse effects including extrapyramidal symptoms and oversedation.[3]

Analysis of patterns of drug use by the elderly also suggests another problem area, that of underutilization. Emerging evidence concerning the efficacy of treatment of mild to moderate hypertension in patients >65 years of age has not yet found a place in the therapy of many older patients with hypertension who might benefit from it. In addition, in a large-scale study of several hundred thousand elderly medicaid recipients, our group has found that available agents that have been shown effective for the treatment of incontinence are strikingly underused in this vulnerable population.[4] Day-to-day experience on a geriatric consultation service makes it clear that however large the group of elderly patients who receive the wrong prescription based on an ill-founded notion of "a pill for every ill," there is an equally worrisome group of patients denied therapy as a result of either ignorance or misguided therapeutic nihilism on the part of their physicians.

Another disturbing line of evidence comes from studies that examined physicians' beliefs and practices concerning use of medication in the elderly. Physicians presented with fairly straightforward questions concerning practical geriatric pharmacology have been shown to have an alarmingly high level of misinformation.[5] In a study we are conducting with Louis Harris and Associates for the John A. Hartford Foundation, we have surveyed 500 physicians in a national sample to determine their knowledge and attitudes concerning specific problems in drug therapy in the elderly. Initial results suggest major gaps in physician awareness of optimal management of arthritis, gastrointestinal symptoms, insomnia, and anxiety in their elderly patients.

Part of the problem is structural and relates to the way medical care is organized and reimbursed. With the notable exception of the American Academy of Family Physicians, virtually no other group requires ongoing demonstration of competence for periodic recertification. State boards of licensure have been notoriously lax in demanding that physicians demonstrate an acceptable level of current knowledge before reli-

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censure, which is to all intents and purposes automatic throughout the country (although this picture is beginning to change somewhat). Unfortunately, litigation seems to be the most actively pursued form of "quality control" in relation to physician prescribing, particularly for this vulnerable group. As a means of developing and maintaining optimal behavior, this trend has all the appeal (and probably all the efficacy) of corporal punishment in grade school.

Nor is it possible to gain solace by looking at the capacity of the elderly to monitor their own therapy. Despite a high level of interest in informing themselves about medications and their use, American patients appear to receive relatively little information, on the average, from physicians or pharmacists about their drug therapy.[6] Misinformation and noninformation are rife, leading to unmeasured (but potentially large) noncompliance and miscompliance. The latter results in an unnecessarily high frequency of drug-related complications in this physiologically vulnerable group.[7]

Vast as these problems are, they are nonetheless amenable to solution. Two approaches, although important, stand apart from the topic of training under discussion here. First, as always, is the need for more research. Considerably more must be learned about the altered pharmacokinetics and pharmacodynamics of drugs in the elderly. Second is the area of regulation. For too long it has been the case that new medications destined for widespread use among the elderly would be tested and approved based on premarketing studies conducted primarily (or even exclusively) in nonelderly patients. Some progress is being made on this long-neglected problem. Product labeling is another area in which both the Food and Drug Administration and the pharmaceutical industry need to do a better job in relation to the elderly. Although some companies have begun to add brief sections concerning use of specific products in the elderly, this is by no means as widespread as it should be. For example, in a current edition of the *Physicians' Desk Reference*,[8] although there are special sections concerning the use of digoxin in pregnant women, nursing mothers, and infants and children, there is no section specifically addressing the use of this drug in the elderly, who account for far more of the use (and adverse effects) of this drug. Similar omissions occur with other medications notorious for their tendency to be problematic in the elderly.

An area overlapping both regulatory and research considerations is that of postmarketing surveillance. Even in a situation of optimal premarketing testing, it is likely that some medications will be found on widespread use to present special problems in elderly patients. This may be the result of an interaction with a medication or coexisting disease that could not have been anticipated in premarketing evaluation of any plausible scale. There does not currently exist any uniform nationwide approach to this problem, although a number of emerging methodologies should make this undertaking feasible. Just as the thalidomide disaster led to a more rigorous concern for the evaluation and approval of medications, the unfortunate events surrounding benoxaprofen (Oraflex) in the elderly might lead to a more proactive system of studying the effects of marketed agents on large populations, particularly including the aged.[9]

Additional education is needed at all levels of medical training from the first-year pharmacology courses to the end of residency. The best approach to postresidency training is more problematic. Leaders in the emerging field of clinical geriatrics have come to the realization that the health care needs of the elderly in this country will not be met through the production of thousands of geriatric specialists annually; a simple comparison of the numbers of trainees and elderly patients makes it clear that this is the only possible viewpoint. However, considerable progress has been made in geriatric medicine through the training each year of a small but robust cadre of researchers/teachers/consultants. Although demand is still far in excess of supply, this "leverage" approach seems to be bearing fruit. A similar approach appears worth pursuing in the area of geriatric pharmacology, as discussed in the other articles in this issue.

However, it will be important that the component disciplines be defined broadly enough so as not to exclude individuals or entire fields of inquiry that are so desperately needed. Specifically, just as it would be a mistake to amputate the disciplines of molecular biology or other laboratory-based research in pharmacology by condemning these fields for being "not clinical enough," it would be equally unwise to sever the opposite end of the spectrum, namely the study of the epidemiologic and even socioeconomic aspects of use of medication in the elderly.[10] These areas offer much promise and relevance for research, training, and care in geriatric and medication use. Rather than being a rite of passage for this new field, such an attempt at circumcision would in fact be a castration.

Some centers will have special expertise in the "bench" end of the geriatric pharmacology spectrum, whereas others might focus more on the epidemiologic/policy end of the continuum, and still others might represent expertise in both kinds of inquiry. Of course, the highest of scientific standards would need to be met in any of these endeavors. The list of questions demanding answers is too large, the demographics too compelling, and the pool of interested applicants too varied and (to be candid) too small to warrant a more restrictive approach. Only a conception of training in geriatric pharmacology that is broad enough to include all of its facets will be equal to the challenge with which this emerging area presents us.

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Medication Use and Geriatrics:

Key Research Areas and Some Examples

Item 5

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INTRODUCTION

The 12% of the U.S. population that is over 65 currently uses about 25% of all health care resources, and about 30% of all prescription medications. These figures will rise more than proportionately as the aged population grows and simultaneously becomes more heavily skewed toward the oldest old. Medications play a central role in the health care of the elderly. They have contributed substantially to adding years to the lives of aging Americans; equally importantly, they have also made a major contribution in "adding life to the years" of the elderly, in reducing symptoms and increasing functional capacity for many chronic illnesses which still elude curative therapy. Nonetheless, the elderly are also at significantly added risk of adverse drug effects. Even in the face of healthy aging, hepatic metabolism, renal excretion, body composition, and receptor sensitivity undergo important changes which impact considerably on the risk of adverse drug effects. The coexistence of multiple illnesses and their corresponding therapies in the elderly compounds this risk dramatically.

Despite the fact that the old are thus the most prominent consumers and beneficiaries of drug therapy, they are also the most likely to suffer adverse consequences if these drugs are used inappropriately. These risks are compounded by several non-pharmacologic factors. Pharmacology and therapeutics have long been an under-represented area in most medical school curricula; geriatrics is presented even more scantily if at all in most American medical schools. Thus, expertise in geriatric pharmacology is very poorly distributed throughout the population of practicing physicians, despite the fact that prescribing medications to patients over 65 is one of the most common and important therapeutic interventions in all of medicine today. This results in a significant amount of under-prescribing, over-prescribing, and mis-prescribing. Older agents are used where newer ones would be more safe and effective; in other patients, important and treatable conditions are left untreated. At the same time, drug therapy may be used where no real indication exists; and the pharmacologic frailty of the elderly is often given inadequate attention in the implementation of therapeutic regimens.

On the patient side as well, the elderly represent special problems in relation to medication use. Compliance is impaired by complex regimens, increased frequency of side effects, and often by co-existing problems such as forgetfulness or outright dementia. Economically, too, the elderly present a uniquely challenging population. Prescription medicines are not covered for most elderly by Medicare, and thus represent one of the largest out-of-pocket health care expenditures for this age group. Ongoing developments in drug entitlements provided by individual states as well as those planned by the Medicare program represent a vast uncharted area of new benefits whose effect on medication use, morbidity, and mortality is still largely unknown.

In view of the central role played by medications and the elderly in the national health care scene, it is surprising how little research has focused on the clinical and policy aspects of geriatric drug use. The purpose of this proposal is to identify representative areas of inquiry in this emerging field, and to suggest ways in which addressing such topics could yield benefits for the health care system as a whole, its various components, and of course the elderly themselves. The emphasis of such research would not be on traditional clinical pharmacology or new drug development, which are the areas in which some progress is currently being made in relation to the elderly. Rather, it would focus on broader aspects of medication use in the elderly, such as pharmaco-epidemiology, health services research, policy studies, and the clinical investigation of old drugs (as opposed to INDs) in old patients. To illustrate each area, at the end of each section is a brief overview of the research activities in our own group that touch on that particular topic to provide an example of one approach to this complex subject.

Clinical Decisionmaking and the Diffusion of Innovation:

While there is a small but growing body of literature on how physicians make clinical therapeutic decisions, virtually none of it addresses one of the commonest decisions in health care: the choice of a medication for a given patient. Considerable evidence exists to indicate that this choice is often made suboptimally, but not enough is understood concerning how this process occurs, and, more importantly, how it can be improved. Central here is the issue of diffusion of innovation: when new insights about geriatric pharmacotherapy are obtained in the laboratory or in randomized clinical trials, how is such information spread to the population of practicing physicians? How can this process be improved, with the most appropriate drug technology delivered to patients at the earliest possible moment? Increasing pressure is brought to bear on physicians to reduce cost, but such pressure (and those who impose it) do not often take adequate account of the clinical consequences of such "savings." While the effect of such actions on the macro level is described further below under Health Services Research, considerable attention needs to be paid to the battleground which represents the ultimate final common pathway of all these vectors: the individual clinical decision made by the physician (or, increasingly, by other health care professionals).

Several studies at the Harvard Medical School Program for the Analysis of Clinical Strategies (HMS-PACS) address this issue. In one, a four-state sample of 435 physicians was randomized to receive mailed drug information, "outreach education" by a medical school-based pharmacist, or no intervention. Our paper on this study in the New England Journal of Medicine reported that the physicians randomized into the outreach education group improved their prescribing significantly, and a benefit-cost analysis of the intervention showed that on an operational level it would save at least $2 for every $1 of program cost. This approach, initially funded by the National Center for Health Services Research, is being adopted by a number of organizations responsible for medication costs, in an attempt to improve the quality and precision of prescribing.

In another NCHSR-supported study, a doctoral student at the Harvard School of Public Health is analyzing the pattern of diffusion of specific medication innovations among physicians treating the elderly (e.g., ACE inhibitors, transdermal nitrates, beta-blockers), in an attempt to learn which physicians use which medication innovations first, and on which of their elderly patients. Another trainee, who is simultaneously receiving a Ph.D. in anthropology and M.D. from Harvard, is studying the decision process in long term care facilities which cause caregivers to apply restraints to patients, either physical or chemical (i.e., psychoactive medications). Finally, in a large multi-year study of 12 long term care facilities in Massachusetts supported by the John A. Hartford Foundation, we are conducting a randomized controlled trial of geriatric pharmacology outreach education for physicians, nurses, and aides to determine whether drug prescribing in such institutions can be improved, and to measure the effect of such changes on the cognitive status and level of disability of patients in the study homes.

Pharmaco-epidemiology:

Despite the fact that the elderly are the most prominent consumers of medications, until recently it has been common for most pre-marketing clinical trials of new agents to focus predominantly on young or middle-aged patients. The results of this have been unfortunate, as in the case of benoxaprofen (Oraflex), which when used in a large population of elderly people proved to have adverse effects that had not been anticipated prior to marketing. One response to this knowledge deficit has been an increasing interest in post-marketing surveillance of drugs used commonly by the elderly. Even in a healthy young population, adverse drug effects which occur only once in every 10,000 or 50,000 patients are unlikely to be detected by conventional Phase III testing. The likelihood of untoward events occurring once a drug is in widespread use are compounded further by the altered pharmacokinetics and pharmacodynamics known to prevail in the elderly, as well as the exponentially increased likelihood of un-studied drug-drug or drug-disease interactions.

Because it is impractical to conduct pre-marketing stüdies that would be large enough to uncover even a portion of all the unanticipated adverse consequences that could occur when a drug is in widespread use among the elderly, a number of researchers in academia, industry and government have become interested in the prospect of performing post-marketing surveillance with large databases which include the experiences of hundreds of thousands of patient-years of exposure. In this way, previously unrecognized adverse effects can be identified early, and defined in relation to other risk factors or dosage regimens which may predispose to their occurrence. In many instances, corrective steps can then be taken in revised labeling and physician or patient education, to prevent the use of what may be an otherwise useful drug in a contraindicated clinical situation. Many observers note that had such surveillance been applied to Oraflex early in its marketing, the adverse effects of diminished clearance by the elderly might have been anticipated, and dosage or indications changed so that considerable morbidity and mortality might have been prevented, and the drug not lost to all subsequent use.

At HMS-PACS, with support from the National Institute on Aging, we have developed a very large database comprising all health care encounters (including prescription medications) for about 1.5 million participants in the Medicaid and Pharmacy Assistance for the Aged programs of the state of New Jersey. Because 40% of the Medicaid budget in most states goes for care of chronically ill elderly, this database is particularly enriched in drug use experiences among the aged. To further increase our capacity to monitor drug-related events in those over 65, we have also obtained all Medicare transactions for every resident of the state of New Jersey. While Medicare does not cover drugs, the unique linkage of the Medicaid, PAA, and Medicare claims files in our system makes possible a robust analysis of the clinical experiences of a very large number of older people. Our earlier work with Medicaid claims data resulted in a paper in the Journal of the American Medical Association which documented an increase in the frequency of treated depression among patients taking beta-blockers. Current research involves an NIA-supported study on rates of falls and fractures in elderly patients taking different antihypertensive or hypoglycemic regimens, and the relationship between the use of nonsteroidal anti-inflammatory drugs and the management of hypertension and congestive heart failure in the elderly.

Health Services Research:

Because the elderly represent such costly consumers of health care, much of which is publicly funded, they have been the target of increasing cost containment efforts, which are bound to intensify further in the coming years as budgetary controls tighten further. Yet there is reason for concern that these cuts often remove as much muscle and bone as they do fat, although the extent of these negative consequences is only now beginning to be documented. Ironically, in at least some instances of across-the-board reductions of programs, it may well turn out that the "savings" achieved by short-sighted cuts may in fact have resulted in increases in health care expenditures, often to the very same agency, as well as extracting an unnecessary toll in human suffering and even mortality. Because these changes are ongoing, there is not yet enough information in the literature to indicate the scope of this potential problem. Nonetheless, future policy, driven by an ever more frantic drive to reduce expenditures, must be informed by such assessments.

At HMS-PACS, we have looked closely at one such attempt at cost containment in the New Hampshire Medicaid program. A grant from the Health Care Financing Administration made it possible to perform computer-assisted analysis of all prescription claims for the state of New Hampshire over a period of four years. Recently, we reported in the New England Journal of Medicine that when a three drug per patient per month limit was imposed by the state regulatory authorities, the reduction in drug use was not confined to marginal or inexpensive medications. Rather, essential medications for the control of hypertension and other cardiovascular diseases, diabetes, and other chronic illnesses were omitted from the regimens of individual patients. We intend next to document the economic and clinical consequences of such drug cutbacks, but the Department of Health and Human Services has not yet provided support for this phase of the research.

In another study, we collaborated with the Massachusetts Department of Public Health in looking at patterns of medication administration and use in the relatively unsupervised sector of "rest home" long term care facilities. That study found a worrisome mismatch of complex patients, powerful medications, and completely untrained staff; it led to a major change in the state regulations concerning medication use in rest homes, and an increase in reimbursement rates for facilities which met higher standards of patient care. In the in-patient arena, HMS-PACS has developed a relationship with the Beth Israel Hospital, one of the major teaching hospitals of Harvard Medical School, which serves as a "clinical laboratory" for our research on in-patient use of prescription medications. Working in cooperation with the hospital's Pharmacy & Therapeutics Committee (chaired by J.A.), PACS is studying ways to optimize the use of medications among acutely ill hospitalized patients while enhancing, rather than threatening the quality of patient care.

In a current NCHSR-funded project, we are analyzing the effect of widespread curtailment of reimbursement in the Medicaid program for a category of drugs (DESI drugs) whose efficacy has been questioned by the Food and Drug Administration. Using the New Jersey Medicaid database described above, we are studying the effect of such reimbursement changes on prescription drug costs and on physician choices among remaining therapies.

Old Drugs in Old Patients:

Despite the abundance of pharmacological research on the pharmacology of new drugs in non-elderly patients, there is a surprising dearth of studies of the adverse effects of familiar drugs in elderly patients. This "knowledge gap" makes it very difficult for the clinician to make reasoned judgements about the relative risks and benefits of, for example, hydrochlorothiazide, propranolol, or enalapril in the management of uncomplicated hypertension in the older patient. As noted above, there is limited relevance to the elderly of pre-marketing clinical studies performed in young patients; the side effect profile may be dramatically different in an older patient, but remarkably little evidence can be found to document this. As interest grows in shaping physicians' clinical choices along certain lines, it becomes increasingly important to document the advantages and disadvantages of various agents (other than cost) in this population. Specific problems of the elderly, such as mental status changes and gait instability, are notoriously absent from evaluations of many medications, even when they focus on the geriatric population.

To help fill this gap, HMS-PACS is engaging in several double-blind placebo-controlled clinical trials of conventional therapies in geriatric patients. In one study supported by the Veterans Administration, a detailed battery of tests for central nervous system side effects is administered to elderly hypertensive patients receiving either a beta-blocker, a thiazide, or placebo. Outcomes measured include memory, attention, mood, reaction time, and other assessments of cognitive or psychomotor function. A similar battery of tests is to be applied to elderly patients receiving topical glaucoma therapy, randomized into those receiving timolol, betaxolol, or placebo. In addition, measures of cardiovascular and pulmonary function are obtained.

To address the very thorny issue of optimal medication use in demented elderly patients with behavior disorders, we are preparing a randomized controlled trial of a benzodiazepine, a neuroleptic, or placebo in several long term care settings. Although the nursing home is the site of some of the most intense prescribing in the health care system, for some of the most disabled patients, remarkably little research on medication use occurs in these settings. In another clinical trial, complementary to the population-based epidemiologic study of non-steroidal effects, we are measuring renal function in elderly patients at a Harvard-affiliated long term care facility in relation to the beginning and continuation of their non-steroidal anti-inflammatory drug therapy.

THE FUTURE

Considerably more work is needed in the area of medication use and the elderly as the health care system confronts both a burgeoning older population and accelerating developments in basic science and new drug discovery. While this confluence of forces will effect every aspect of health care, it will be most prominent in the following areas: neuroscience and psychopharmacology, particularly in relation to Alzheimer's disease and psychoactive therapies; cardiovascular disease, including hypertension, still the most important cause of morbidity and mortality in this population; and degenerative chronic disease, particularly arthritis, which while not an important cause of death, is responsible for an increasing burden of functional incapacity as the population ages.

A number of important new issues need to be addressed in this field. A small sample of these follows:

- How have patterns of medication use by the elderly changed in the past decade, and what does this imply about future patterns of medication use in this group?
- What ongoing developments in demographics and in basic science can be expected to shape the use of medications by the elderly in the next century?
- What is the most appropriate way to study both new and "proven" medications in the elderly so as to monitor the important areas of functional capacity and cognitive function which are often neglected in conventional drug evaluations?
- How can such insights inform the integration of "quality of life" considerations into drug therapy decisions at both the individual and policy levels?
- What is the most accurate and efficient means of conducting large-scale post-marketing surveillance of medications in the elderly to serve as an "early warning system" for adverse effects in this vulnerable population?
- What has been the impact of recent drug benefit programs for the elderly established by several states, and what can be learned from this experience to extrapolate to the impending coverage of medications by the Medicare program?
- What other reimbursement and regulatory developments are likely as payors in both the public and private sector attempt to address the increasing need for drug coverage of the elderly in a cost-effective manner?
- What is the best way to impact on the clinical decisionmaking of an individual physician caring for an individual elderly patient, so as to maximize the technology transfer from laboratory and clinical trial to actual practice, and how will this be effected by evolving patterns of health care organization and financing?

A coordinated approach to this field is both necessary and feasible. Ultimately, a stronger knowledge base, carefully conducted policy analyses, and innovative programs represent the most effective way of addressing this growing health care need of the nation's elderly population.

Item 6

POST-MARKETING SURVEILLANCE OF MEDICATIONS IN THE GERIATRIC POPULATION

Prepared for The Institute of Medicine
Forum on Drug Development and Regulation

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Harvard Medical School

The issue of post-marketing surveillance in the elderly represents a particularly appropriate area for consideration by members of this group. Even if the elderly were well represented in pre-marketing clinical trials (a goal that is still distant, but toward which some progress is being made), it would never be feasible to include in Phase III studies all of the important and complex combinations of coexisting illness and concurrent medications which are certain to occur when large numbers of older patients begin taking a marketed product on a large scale. Lack of capacity to identify such problems quickly after they occur can result in unnecessary morbidity and even mortality. These in turn can lead to costly litigation, the large-scale "un-marketing" of a given product, and in some cases its abrupt withdrawal from use. Early analysis of such population-based adverse effects information might in some cases lead to a change in labelling, dosage, or physician education, one could prevent the complete forfeit of the enormous sums required to bring a drug to market.

The increasing sophistication of computer hardware and software has made it possible to collect and analyze data for very large populations, containing detailed linked records of both medication use and clinical events. Although this emerging methodology has important limits as well as strengths, it does make possible close surveillance of marketed drugs in elderly populations. The increased need for such research in the aged is evident from their well-documented changes in pharmacokinetics and pharmacodynamics, and their markedly higher frequency of co-morbidity and polypharmacy. Fortunately, automated databases can take advantage of the high representation of elderly in such programs as Medicaid, Medicare, and state-run drug programs for the elderly. As an example, we have developed such a database linking each of these elements for one state, covering all medication and other health care experiences of a population of about 1.4 million people. When unexpected emergencies occur (either clinical or man-made, as in the case of benoxaprofen or piroxicam, respectively), the ready existence of such databases can provide sound information on the actual frequency of any adverse effect under study. This makes possible the sober, scientific analysis of risks in a quantitative way, overcoming both the "floating numerator problem" of spontaneous adverse reaction reports as well as the very real risk of "regulation by anecdote" that can occur in an environment starved of epidemiologically sound data.

While efficient to use, such databases are costly to establish and to maintain current. In this regard, they are much like a sort of intellectual fire department which is invaluable when needed, but which cannot suddenly be brought into existence at the first sign of smoke. The cultivation of such databases and the environments necessary to nurture them represents an opportunity for proactive cooperation among industry, regulators, and universities, to create a situation of benefit to all. Indeed, important steps have been taken in all three sectors in this direction, but there is still a long way to go. The Forum could make a major contribution by addressing this issue as a group as well as within its respective constituencies, to make the possibility of large-scale post-marketing surveillance of medications in the elderly a reality and not just an intriguing theoretical possibility.

Item 7

Brief Report

The Importance of Adverse Reaction Reporting by Physicians

Suprofen and the Flank Pain Syndrome

Allen C. Rossi, DDS, MS; Lynn Bosco, MD, MPH; Gerald A. Faich, MD, MPH; Ann Tanner, RPh; Robert Temple, MD

The role of spontaneous reporting in detecting the suprofen-associated flank pain syndrome was examined, including the specific effect of the "Dear Doctor" letter in accelerating the information-gathering process once the initial signal was generated. We believe this to be a noteworthy example of the ability of spontaneous reporting to produce a timely and unequivocal signal of drug-related risk. It also serves to demonstrate the need for vigilant postmarketing surveillance for all newly marketed drugs in the United States, even though considerable premarketing and postmarketing drug experience may exist from use in countries outside of the United States.

(*JAMA* 1988;259:1203-1204)

ON MAY 15, 1987, McNeil Laboratories announced the suspension of suprofen (Suprol) sales in the United States (statgram from McNeil Pharmaceutical, Spring House, Pa, to 730 000 US physicians, dentists, podiatrists, and pharmacists). This decision was said to be based on the low levels of use in the United States; use had fallen because of suprofen's association with more than 300 reports of flank pain and transient renal failure, a pattern subsequently described as the flank pain syndrome (FPS).[1] The decision was undoubtedly also influenced by recommendations made two days earlier by a committee of the European Common Market nations to suspend current authorizations for suprofen's use among member countries. The syndrome was detected rapidly in the United States through reporting by physicians and other health care providers, showing that spontaneous reporting can lead to quick and effective detection of important new drug risks of this type.

This article reviews briefly several important aspects of the development of information about suprofen. First, it examines what was learned about suprofen's safety profile prior to its approval in the United States. Next, it summarizes the process of detecting FPS in the United States, including the special role of the "Dear Doctor" letter in accelerating the collection of information. It also comments on the apparent paucity of data about FPS before its marketing in the United States and provides information concerning how physicians may conveniently report observations to the Food and Drug Administration (FDA) to assist in the postmarketing surveillance of newly approved drugs.

Information From the Clinical Trials and European Marketing Experience

Suprofen is a nonsteroidal anti-inflammatory drug with properties generally similar to other members of its class. It was developed in Belgium, first introduced to the market in Europe in 1982, and eventually marketed in 24 countries for the treatment of pain and arthritis. Suprofen was approved in the United States on Dec 24, 1985, for use in mild to moderate pain and primary dysmenorrhea. Clinical trials involving 2500 to 3000 patients formed the basis for suprofen's approval in Europe; an additional 2100 patients participated in the US clinical studies, including some 800 patients who had received treatment for a period of at least one week. At the time of US approval, suprofen appeared to share a common adverse reaction profile with most other nonsteroidal anti-inflammatory drugs, the identification of chemical cystitis being the only unusual adverse reaction of suprofen recognized up to that time. Neither the European and US clinical trials nor European postapproval use for more than three years provided any identified clues to what would be learned from the US postmarketing experience during a much shorter period of time.

Reporting of FPS in the United States

Following its approval in December 1985, suprofen was first marketed in the United States in January 1986. Promotional efforts included extensive distribution of product samples to prospective prescribers.

The first two known cases of suprofen-related FPS in the United States occurred in February 1986, although neither was actually reported until early May. Each involved a healthy male medical professional who was not ordinarily the sort of patient considered at greatest risk of an adverse drug reaction. The FPS began with the onset of abrupt pain resembling that of renal colic and occurring within 90 minutes to five hours after taking two capsules. This, too, was a common feature of most cases. After the first five or six cases—some with evidence of reduced kidney function—were reported, discussions between the FDA and the manufacturer (in mid-March) led to the decision that the manufacturer issue a Dear Doctor letter to more than 170 000 office-based practitioners in late April. By late June, the FDA had received a total of 117 reports of FPS, which now clearly indicated that a number of patients experienced transient renal failure commonly accompanied by hematuria. Eventually, well over 300 cases of FPS would be reported.

Pattern of Case Reporting and the Impact of the Dear Doctor Letter

The Figure graphically portrays the pattern of reporting cases of FPS during the 17 months of suprofen's US marketing history.

For 291 of the 366 cases reported, information with regard to the actual onset date of FPS was provided. The date of receipt of each report was the month during which the FDA actually received each report either from the manufacturer or directly from the practitioner. It is thus possible to trace the

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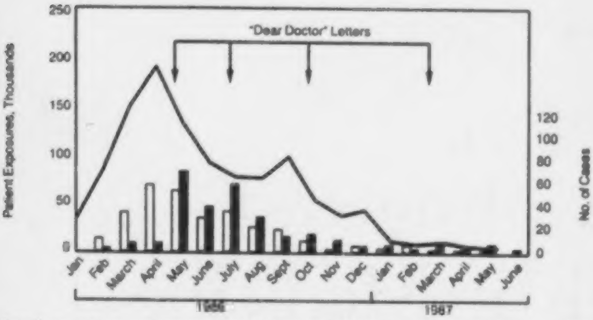
The opinions expressed herein are those of the authors and do not necessarily represent those of the Food and Drug Administration.

Reprint requests to the Division of Epidemiology and Surveillance (HFN-730), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857 (Dr Rossi).



Suprofen use and reports of associated flank pain syndrome. Solid line represents suprofen use; open bars represent adverse drug reactions by month of onset; and filled bars represent adverse drug reactions by month of report.

reporting pattern either by each report's entrance into the FDA's Spontaneous Reporting System database or, for 291 cases, by when the event actually took place. Using the manufacturer's estimates of suprofen use over time,[2] it is possible to derive rates of reported events reflecting either when the events actually occurred or when they were reported.

The data presented in the Figure may be interpreted as showing the following:

1. For the months prior to receipt of the first Dear Doctor letter by practitioners in late April or very early May, the reporting of cases lagged behind their actual occurrence. This delay in reporting, a recognized feature of spontaneous reporting, created a diminished estimate of risk compared with what was actually occurring during this period. Nonetheless, a sufficient number of cases were reported to provide an appropriate signal of the problem within two months of marketing.

2. The effect of the April Dear Doctor letter on increasing the rate of reporting and accelerating the process of information gathering is clear. If only absolute numbers are considered, May reporting provided from four to five times as many cases as the preceding four months; correcting for use, the reporting rate in May (2.4 cases per 10 000 patient exposures) was five to ten times as great as in previous months. It is also apparent that the Dear Doctor letter stimulated the reporting of new cases, as well as the retrospective reporting of cases that had occurred during the previous several months but had either gone unrecognized as a drug-related event or were recognized but not reported. Subsequent Dear Doctor letters (on July 10, 1986, Oct 10, 1986, and March 11, 1987) had a progressively diminishing effect on the numbers of reports received, which, by October, were largely determined by materially decreasing patient exposure to suprofen.

3. When the drug-exposure information is compared with the occurrence dates of cases of FPS during the first several months, a correlation between the two becomes obvious, with cases of FPS increasing in proportion to suprofen use. This tended to support the belief of a causal connection. Unquestionably, the first Dear Doctor letter markedly reduced the use of the drug. Until May, suprofen use was approximately doubling each month; in May, there was a 30% drop in estimated patient exposures from the previous month, which then continued to drop at about the same rate into June. There followed a period of reasonably stable use until October, when the third Dear Doctor letter was issued. Thereafter, suprofen use declined until its withdrawal, although the reporting rate of FPS stabilized at about one report per 3500 patient exposures throughout this period.

Comment

The role of spontaneous reporting in the identification of this syndrome was noteworthy. The signal it generated was timely and unequivocal and the information produced established causality with reasonable certainty. Spontaneous reporting also seemed to have identified users at highest risk. Several characteristics of the adverse reaction made such prompt detection by spontaneous reporting possible. The event was unusual in the population not treated with suprofen and occurred abruptly after one or two doses, both features that would point to a causal relationship to suprofen; it involved healthy young individuals with little complicating disease or confounding exposures to consider; and finally, it occurred with uncommon frequency in health professionals, ie, in the people best prepared to recognize, attribute, and report a drug reaction, presumably because of their ready access to drug samples. Indeed, health professionals, their employees, and their spouses accounted for about 40% of the cases of FPS occurring from February to July 1986 and about 25% of all cases of FPS reported during the 17 months of marketing.

What remains a mystery is why FPS was not recognized in postmarketing experience outside of the United States. Prior to US approval and marketing, sufficient time and exposure would seem to have taken place to have allowed its detection, especially in countries like the United Kingdom, where an excellent system for spontaneous reporting exists. Yet only three cases were eventually identified in the United Kingdom and only 19 cases in all of the countries outside of the United States in which suprofen had been approved. A different pattern of use in these countries, involving a smaller proportion of exposures in the high-risk category (ie, men less than 40 years of age), might explain some of the difference but is unlikely to explain it all. For the time being, at least, the answer is not apparent. What is certain, however, is the need for vigilant postmarketing surveillance for newly marketed drugs in the United States, despite the availability of considerable premarketing and postmarketing experience with the drug both within and outside of the United States.

We continue to urge all physicians and other health care providers to report their unusual observations, particularly involving newly approved drugs, to the FDA, whether or not they are certain a causal connection exists.[3,4] For their convenience, an Adverse Reaction Report form (FDA-1639b) now appears on the last page of most editions of the 1987 *Physician's Desk Reference*[5] and of recent editions of the American Medical Association's *Drug Evaluations*.[6,7] This form may be photocopied for repeated use.

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Item 8

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Special Report

Adverse-Drug-Reaction Monitoring 1589
Gerald A. Faich

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NEJM

MEDICAL COLLEGE OF GEORGIA

The following courses will be offered by the College in July: "Clinical Genetics" (July 7–9), and "Medical Oncology and Hematology — Recent Advances" (July 9–12).

Contact the Div. of Continuing Education, Medical College of Georgia, Augusta, GA 30912-6450, or call (404) 828-3967.

PULMONARY CIRCULATION

A course entitled "Pulmonary Circulation in Health and Disease" will be offered at the Wisconsin Center in Madison, July 8–11.

Contact Sarah Z. Aslakson, Continuing Medical Education, University of Wisconsin, 465B WARF Bldg., 610 Walnut St., Madison, WI 53705; or call (608) 263-2856.

CALL FOR PAPERS

Abstracts are now being accepted for the second International Conference on Pharmacoepidemiology, entitled "Population Based Data Systems Linking Drugs, Medical Care and Disease," to be held in Minneapolis, September 10–12. The deadline for receipt of applications is July 1.

Contact Dr. Stanley A. Edlavitch, Div. of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN 55455, or call (612) 624-4426.

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The University will offer a course entitled "Curriculum for the Hearing Impaired" at the Governor Baxter School for the Deaf on Mackworth Island, Me., July 7–11.

Contact Barbara McGough, University of Southern Maine, 400 Bailey Hall, Gorham, ME 04038, or call (207) 780-5326.

SPECIAL REPORT

ADVERSE-DRUG-REACTION MONITORING

The U.S. Food and Drug Administration (FDA) has long been conducting a program to monitor reported adverse drug reactions to approved drugs. The purpose of this paper is to review the rationale for monitoring adverse drug reactions, to describe the current program, and to encourage physician participation in the program. The program began in the late 1950s, after the registration by the American Medical Association of cases of aplastic anemia due to chloramphenicol.[1] It expanded greatly when the 1962 revision of the Food and Drug Act required the pharmaceutical industry to report adverse drug reactions to the FDA. Since 1969, data from the program have been entered into a computer, and more than 280,000 reports have accumulated in the data base. In recent years, the discovery of major safety problems after marketing, as in the cases of zomepirac (Zomax) and benoxaprofen (Oraflex), has led to increased attention to the monitoring of adverse drug reactions.

Background

Pharmaceutical products undergo extensive and costly testing and review before marketing. Approval for marketing is primarily based on well-controlled clinical trials to demonstrate efficacy and safety. Thus, when the marketing of a drug begins, there is already considerable evidence that it will be useful while not causing unacceptable harm.

However, it must be recognized that preapproval testing cannot provide complete assurance of safety or information about all effects. This is because of several practical limitations in the conduct of human trials.[2,3] Such trials seldom involve more than 2000 patients or last longer than three years. Thus, they may not detect very uncommon side effects[4] (e.g., anaphylaxis caused by zomepirac[5]) and delayed effects of long-term administration (e.g., cervical cancer associated with the use of oral contraceptives[6]). Important adverse reactions discovered after marketing may occur at a rate of 1 in 10,000 prescriptions (e.g., pseudomembranous colitis following the use of lincomycin[7]) or less. Most patients enrolled in clinical trials have relatively uncomplicated disease and are drawn from restricted age groups. Thus, preapproval data often do not apply to pregnant women, children, elderly persons, and patients with complicated diseases who require treatment with multiple drugs. Yet, these groups may well be exposed to a drug after marketing begins.

Because of the inherent shortcomings of preapproval clinical trials, postmarketing surveillance is crucial for providing additional safety information that cannot be realistically collected before approval of the drug.[8-13] "Surveillance" in this context may be defined as the systematic detection of drug-induced reactions by practical, uniform methods. Its overall purpose is to provide new information on drug risks, and it includes the analysis of collected data and the dissemination of this information. Data from surveillance of the actual use of drugs in medical practice are routinely used as a basis for modifications in drug usage and for making new estimates of risk. One key aspect of postmarketing surveillance is the maintenance of a system for the reporting of adverse drug reactions.

The collection and analysis of reports on adverse drug reactions is important because such reports provide early warnings of previously undetected, serious drug risks. If such monitoring had been done in Europe in the late 1950s, the discovery of teratogenicity due to thalidomide[14] would have occurred much earlier than it did. Analyses of the adverse-reaction monitoring program at the FDA have shown that it can generate postmarketing data as effectively as can many structured and costly postmarketing studies.[15,16] It has been noted that "most unexpected ADRs [adverse drug reactions], in fact, are turned up by voluntary reporting" and that "reporting by physicians remains the single most important source of suspected ADRs."[8] Lasagna recently stated, "Spontaneous reporting by the alert and competent doctor will, for the foreseeable future, remain the most important source of new leads about drugs."[17]

Structure of the Adverse-Reaction Monitoring Program

FDA monitoring of adverse reactions is primarily based on "spontaneous" reports from practicing physicians — i.e., reports that originate from observations made in the usual practice of medicine (not derived from a formal study). Spontaneous reports reach the FDA through either the drug manufacturers or direct contact by physicians. When a physician notifies a manufacturer about a possible reaction, the manufacturer is required by law and regulations[18] to report this observation to the FDA. Direct reporting to the FDA is encouraged by the distribution of a report form that is mailed to nearly all physicians in the United States several times a year in the *FDA Drug Bulletin*.

For an adverse-reaction report to be interpretable, it must contain descriptions of the reaction, the exposure to the drug, the temporal relation between exposure and reaction, and the underlying disease. When the FDA receives a report, it assigns standard terms to the description of the reaction[19] and enters the report into its computer data base. Every direct report from a physician and all manufacturers' reports of unexpected serious reactions are individually reviewed. The review includes a check to determine whether the reaction is already listed in the drug's package insert, an assessment of the severity of the reaction, and a preliminary assessment of the probability that the reaction was related to the drug exposure. For screening purposes, a reaction is generally considered serious if it resulted in death or hospitalization. When the reaction is deemed serious, the possibility of such a reaction had not been mentioned on the package insert, and the reaction may be related to the exposure to the drug, the computer file is searched for similar reactions. After consultations with epidemiologists, pharmacologists, and others, decisions are made about the degree of intensity of follow-up.

Detailed analyses are carried out for reactions that may indicate important, previously unknown risks. These analyses may include the development of a profile of all reported reactions to the specific drug involved, calculation of reporting rates relative to use of the drug, comparisons with adverse-reaction profiles of other drugs in the same therapeutic class, an examination of premarketing adverse-reaction data, and quantitation of the relation of the drug to the reaction, with the use of epidemiologic data bases.

In addition to reviews of individual reports, quarterly and annual tabulations are done for recently approved drugs and for drugs that are a source of suspicion. These compilations are analyzed for patterns of concern.

SUMMARY OF 1984 ADVERSE-REACTION REPORTS

In 1984, 26,753 spontaneous adverse-reaction reports from individuals or manufacturers in the United States were received by the FDA. Ninety percent of these reports came through manufacturers, and the rest came directly from health care providers. Twenty-four percent of the reported reactions were classified as serious because they involved hospitalization (18 percent) or death (6 percent).

Between 1980 and 1983, 41 drugs that were classified as new chemical entities were initially marketed and were each prescribed at least 100,000 times, according to the National Prescription Audit (purchased from IMS America, Ambler, Pa.), or were used frequently in hospitals. Of the 26,753 reports in 1984, 5230 (20 percent) identified 1 of the 41 new chemical entities as the suspect agent. Since about 85 million prescriptions were written for these 41 drugs, whereas about 1.5 billion prescriptions were written for other drugs, the adverse-reaction reporting rate for the new drugs (62 per million prescriptions) was four times higher than that for other drugs (15 per million prescriptions). The severity of the reactions described in the reports on the new drugs did not differ substantially from that mentioned in the reports on other drugs (Table 1). In addition, little difference in the description of the severity of the outcome of reactions to the new drugs was found in comparisons between direct reports from physicians and those from manufacturers. Zomepirac and benoxaprofen have been excluded from these analyses because the reporting patterns for those agents were atypical.

An analysis of the distribution of adverse-reaction reports according to the therapeutic class of the suspect drug and the extent of its use was revealing. In an evaluation that employed the FDA groupings of therapeutic classes, it was found that the distribution of adverse-reaction reports roughly parallels the extent of use of the drugs, as derived from evaluation of the National Prescription Audit, except in the case of the nonsteroidal antiinflammatory drugs (Fig. 1; "Arthritis" column). These agents accounted for 21 percent of the adverse-reaction reports but for only 5 percent of outpatient prescriptions. This may be partly explained by intensive manufacturer surveillance and reporting on drugs in that therapeutic class.

USES AND LIMITATIONS OF DATA ON ADVERSE DRUG REACTIONS

National surveillance of adverse reactions is a complex process because of the volume of drugs involved and the need to assess causality and risk. Nearly 1.6 billion prescriptions for more than 30,000 drugs are written each year in the United States (National Pre-

Table 1. Distribution of Spontaneous Adverse Drug-Reaction Reports on New Chemical Entities, According to Origin and Reaction Outcome.*

OUTCOME OF REACTION	ORIGIN OF REPORT		
	MANUFACTURER	HEALTH CARE PROVIDER	TOTAL
		no. (%)	
Hospitalization, no death mentioned	889 (18)	87 (22)	982 (19)
Death, with or without hospitalization	222 (5)	20 (5)	243 (5)
No mention of hospitalization or death	3703 (77)	296 (73)	4005 (76)
Total	4814 (100)	403 (100)	5230 (100)

*Figures are from 1984 reports in the United States. The source is the Office of Epidemiology and Biostatistics, U.S. Food and Drug Administration.

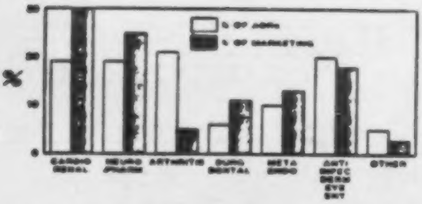

Figure 1. Percentage Distribution of Reports on Adverse Drug Reactions (ADRs) and Market Share of Drugs in 1984, According to Therapeutic Class.

scription Audit), and about 200 new prescription drugs are approved. About 20 of these approved drugs are new chemical entities; the remainder are reformulations and other modifications of known chemicals.

In spite of this complexity, the monitoring of spontaneous reports has, at times, directly resulted in changes in recommendations for use and drug availability. Generally, the reactions involved in such instances are distinct clinical entities that are reported at rates much higher than expected. Recent examples include teratogenesis caused by isotretinoin (Accutane)[20] and toxic epidermal necrolysis associated with pyrimethamine–sulfadoxine (Fansidar).[21] Other examples of adverse reactions that were discovered by means of spontaneous reports include phenformin-induced lactic acidosis,[22] hepatic tumors associated with oxymetholone,[23] and hepatic failure associated with ticrynafen.[24]

Adverse-reaction monitoring can also provide a profile of the types of reactions that may be occurring to one drug or a group of drugs. For example, analyses of reports on nonsteroidal antiinflammatory drugs show that rates of hematologic reactions are higher for oxyphenbutazone and phenylbutazone than for other such drugs.[25] Similarly, the highest proportion of anaphylactic reactions to nonsteroidal antiinflammatory drugs occur with benoxaprofen and zomepirac.

A third use of data on adverse drug reactions is to provide information on patient risk factors. For example, most reports that have associated aplastic anemia with phenylbutazone involved elderly women; this association was confirmed in an epidemiologic study by Inman.[26]

Despite their usefulness, one or even many reports of adverse reactions often do not provide sufficient information to confirm that a drug caused the reaction.[27] A reaction may be caused by the suspect drug, another drug that a patient is taking, or the underlying diseases for which the drug was prescribed; it may also be entirely coincidental.[28] Thus, adverse-reaction monitoring should be viewed primarily as a means for identifying potential problems. Confounding is particularly likely when the drug exposure and the outcome are relatively common. In the case of doxylamine–pyridoxine (Bendectin), for example, there were large numbers of reports of congenital defects associated with exposure to the drug, simply because there was widespread use of the drug during pregnancy; the coincidental, noncausal nature of the association appears to have been demonstrated.[29]

A further limitation of the use of adverse-reaction data results from the underreporting of reactions and the various biases that affect reporting. Medical or mass media attention can stimulate reporting in a distorted manner. In addition, some adverse reactions are more likely to be diagnosed and reported than others because of their known associations with drugs. For example, aplastic anemia is far more likely to be attributed to a drug exposure and reported than is a more common disorder, such as myocardial infarction. For these reasons, it has to be remembered that reporting rates do not necessarily reflect occurrence rates. Consequently, reliable risk estimates cannot usually be made from spontaneous adverse-reaction data alone.

Postmarketing monitoring of adverse reactions should be viewed as one component of pharmacoepidemiology.[30] Both monitoring and epidemiology are based on the nonexperimental collection of observed data on exposure and outcome. Interpretation of adverse-reaction data, like interpretation of other epidemiologic information, must take into account the rates of exposure and possible confounding factors. Often, possibilities derived from reaction monitoring must be tested with use of analytical epidemiologic techniques, including case–control and cohort studies.[31,32]

EFFECT OF ADR REPORTING

How is information on adverse drug reactions actually used? After sufficient evidence is gathered, several mechanisms are employed to modify prescribing practices. New information may be added to the package insert of the product to guide providers.[16] In other instances, the availability of the product may be restricted because of either voluntary withdrawal from the market (as occurred with zomepirac)[5] or recall (as in the case of phenformin).[22] Dissemination of new safety information also occurs by means of the *FDA Drug Bulletin* and the medical literature.

There is no fixed formula for regulation of drug safety because risks must always be balanced against benefits. The severity of the disease being treated and the availability of alternative therapy must be considered. In the case of isotretinoin, for example, how should the risk of teratogenesis be weighed against disfiguring acne and its attendant psychological effects? These are not easily resolved issues, but the starting point is to gather data on risks and benefits. The FDA uses its internal staff and advisory committees to analyze these data and determine appropriate action.

ROLE OF THE PHYSICIAN

Ultimately, the value of any surveillance system is determined by the nature and volume of the reports it receives. The rate of adverse-reaction reporting in the United States is far below that in many other developed countries.[33] To improve reporting, revised regulations[18] and guidelines have clarified reporting requirements and procedures for manufacturers. The FDA has also sponsored pilot studies in Maryland and Rhode Island that are aimed at stimulating direct reporting by physicians.

Physicians in practice must recognize that all the effects of new drugs have not been elucidated at the time of marketing. Much of the development of knowledge about adverse effects depends on the ability of individual physicians to detect these effects and to make preliminary attributions to the drug when appropriate. The FDA and the medical community share the responsibility for providing continual evaluation of drug performance after marketing. If the medical community and patients are to benefit from the experience of individual physicians, suspected reactions must be reported.[34,35] Indeed, "supplying information on suspected adverse reactions is as much a moral duty for the physician as are other aspects of patient care."[36] This is particularly true in the case of serious reactions to new drugs, regardless of whether such reactions have been mentioned in the package inserts.

A number of factors may inhibit physicians from reporting adverse reactions they have observed.[37] The most important may be the lack of knowledge that a reporting program exists and the lack of readily available report forms. Physicians are urged to keep blank copies of the report form that is mailed to them by the FDA. Another inhibition may be concern about possible litigation related to an adverse-reaction report. However, it must be remembered that the adverse-reaction surveillance program is designed to detect possible safety problems with drugs and that the submission of a report does not constitute a legal claim or an acceptance of causality. Because the identities of the reporters and the patients are kept confidential by the FDA, individual reports have little value in the courtroom. The desire to publish may also inappropriately inhibit early reporting to the FDA. Authors are urged to send in early notification of adverse reactions to the FDA, while articles are being prepared or are in press.[34,38] Physicians need to be assured that their reports are important and that they are used.[39]

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Item 9

MEDICAL CARE
February 1988, Vol. 26, No. 2

Prescription Drug Use in 1984 and Changes Over Time

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JOHN P. JUERGENS, PHD, AND GERALD A. FAICH, MD, MPH

More than 1.5 billion prescriptions were dispensed from retail pharmacies in 1984 at a consumer cost of $18.4 billion. The number of prescriptions dispensed in 1984 equaled the previous record set in 1973. Over 40% of 1984 prescriptions were for four therapeutic classes: cardiovascular drugs, anti-infectives, psychotherapeutic drugs, and diuretics. Prescriptions for cardiovascular drugs and diuretics increased substantially from 1975 to 1984, while prescriptions for psychotherapeutic drugs decreased. Outpatient use of systemic antiinfectives remained fairly stable over the 10-year period. Trends in the use of specific drug categories within these broad therapeutic classes were variable, as were patient age and sex distributions. Key words: drug utilization; prescription drug use; cardiovascular drugs; diuretics; anti-infectives; psychotropic drugs. (Med Care 1988; 26:105–114)

Although prescription drugs are widely used in the United States, published data on national patterns of drug use are relatively scarce. Most studies are limited to a single drug class, medical care setting, or geographic region, and often focus on drug costs rather than drug exposure. National estimates of drug use provide valuable comparison data for those studies limited to one area. They also provide a broader context for assessing misuse or appropriateness of therapy and identifying potential problems with specific drug classes such as psychotherapeutic drugs or antibiotics. Examining drug use patterns over time provides insight into changing disease and therapeutic aspects of medical care.

Data on outpatient use of all prescription drugs are continuously collected from physician and pharmacy panels and extrapolated nationally by pharmaceutical marketing research companies. The United States Food and Drug Administration (FDA) subscribes to three pharmaceutical marketing research data bases. These data bases are used to assess drug exposure for a variety of issues, including development of recommendations on the quantity of controlled substances to be produced, the use of denominators in epidemiologic studies, and the production of descriptive studies.[1,2]

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The opinions expressed in this article are those of the authors and not necessarily those of the FDA. The authors assume responsibility for the accurate transcription of all IMS data and the mathematical calculations performed by the Office of Epidemiology and Biostatistics.

Portions of the data in this article were presented at the American Public Health Association Meeting, Washington, DC, November 1985. Data were also included in *Drug Utilization in the U.S.—1984: Sixth Annual Review* (March 1986), an FDA technical report that is distributed internally and deposited with the National Technical Information Service.

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The present article provides information on overall prescription drug use in 1984 and changes in outpatient drug exposure from 1971 to 1984. More detailed information is presented for cardiovascular drugs, diuretics, systemic anti-infectives, and psychotherapeutic drugs, including the types of drugs most commonly used within each therapeutic class, the age and sex of patients for whom these drugs are prescribed, and 10-year trends in prescription volume.

Data Sources

All drug utilization data were derived from two of the pharmaceutical marketing data bases purchased by FDA from IMS America Ltd.: the *National Prescription Audit* (NPA)[3] and the *National Disease and Therapeutic Index* (NDTI).[4] The current study used NPA data to assess prescription volume and NDTI data to identify the age and sex distributions of users. The IMS data bases combine individual drugs into therapeutic groups by the Uniform System of Classification (USC).[5] The data bases and classification system are described in more detail below.

National Prescription Audit (NPA)

The NPA provides information on prescriptions dispensed by chain and independent pharmacies in the contiguous United States. Other outlets such as discount stores and supermarkets with pharmacies are not included. NPA methodology has not been consistent over time. Prior to 1981, data were obtained from a representative sample of 800 pharmacies, each of which was audited for 2 days per month. Since 1981, IMS has received monthly data tapes on prescriptions dispensed by a panel of 1,200 computerized pharmacies. The panel does not represent a true random sample; however, IMS does ensure that the panel is representative of United States pharmacies in terms of region, type of ownership, and size. IMS also revised the NPA extrapolation methodology at the end of 1983.

The 1981 and 1983 methodologic revisions resulted in significantly different estimates for some individual drugs and a few therapeutic categories (e.g., oral contraceptives). However, the broad therapeutic classes discussed in this article were less seriously affected. As shown in Figures 1–5, data points for 1981 and 1983 (revised data in all cases) were not particularly discrepant from the general trend lines.

National Disease and Therapeutic Index (NDTI)

NDTI estimates are based on information received from a panel of more than 2,000 office-based physicians in 19 major specialties. These physicians report case history information on each of their patients they see or contact in any way, regardless of location (e.g., in the office, in the hospital, over the telephone).

NDTI drug reports do not equate exactly to written prescriptions: only about 59% of the drugs recorded during a physician–patient contact in 1984 involved issuance of a formal prescription (with the remainder representing drugs that were administered directly, given as a sample, or recommended by the physicians, in addition to drugs they prescribed for patients in hospitals or nursing homes). In addition, refill prescriptions not involving a physician–patient contact are not captured by the NDTI, leading to an underestimation of chronic therapies if drug reports are viewed as prescriptions. By convention, the NDTI employs the term "mentions" for such reports: *"mentions" reflect usage, but should not be interpreted as directly equivalent to prescriptions or patients.* Mentions represent drugs prescribed, recommended, or given in any medical setting by private physicians in office-based practice.

Uniform System of Classification (USC)

The USC was developed through a joint effort of the Pharmaceutical Manufacturers Research Group and IMS America Ltd. to provide a basis for grouping drug products

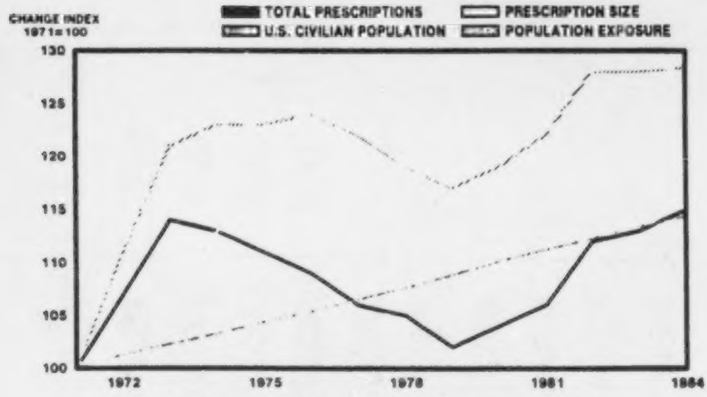

FIG. 1. Prescriptions, population, and outpatient drug exposure, 1971–1984.

into therapeutic categories. As a hierarchical system, the USC allows us to assess drug use at varying levels of specificity such as the broad level of major therapeutic classes (e.g., cardiovascular drugs) and more specific drug categories within the therapeutic class (e.g., beta blockers, vasodilators).

The values of using a standardized drug classification scheme have been enumerated elsewhere.[6] Although any standardized system will inevitably contain aspects that may seem inappropriate to the individual researcher, the benefits of using such systems generally outweigh the advantages

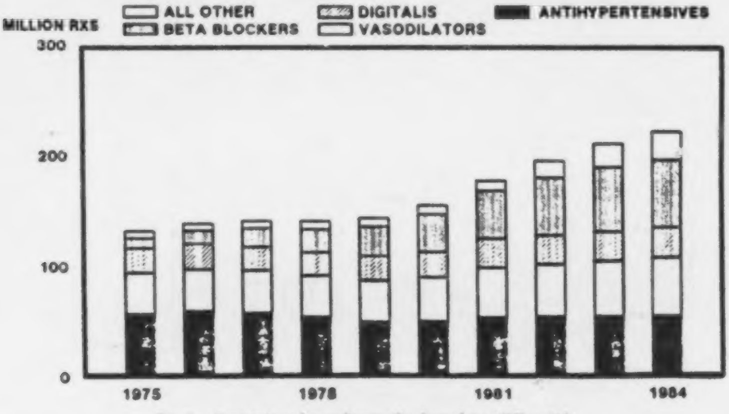

FIG. 2. Prescriptions for cardiovascular drugs from 1975 to 1984.

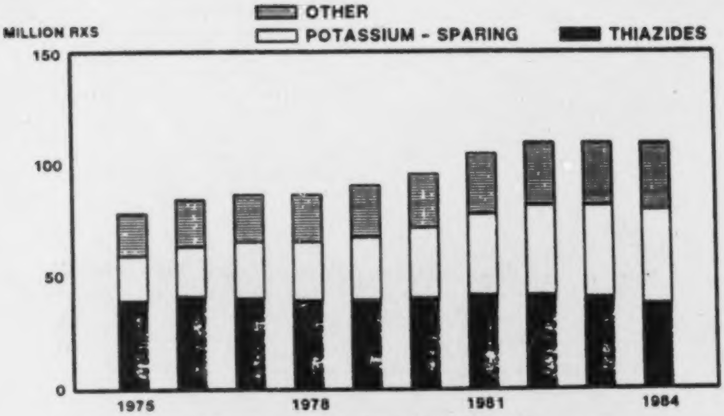

FIG. 3. Prescriptions for diuretics from 1975 to 1984.

of devising study-specific classification schemes. All data in this article are grouped by the USC. Use of sedative-hypnotics is not included in the data on psychotherapeutic drugs since the USC considers them to be two separate therapeutic classes. Similarly, diuretics are not included with cardiovascular drugs. USC terminology is also used throughout, although this may seem inappropriate in certain instances. For example, "major tranquilizers" are more commonly called neuroleptics or antipsychotic drugs,

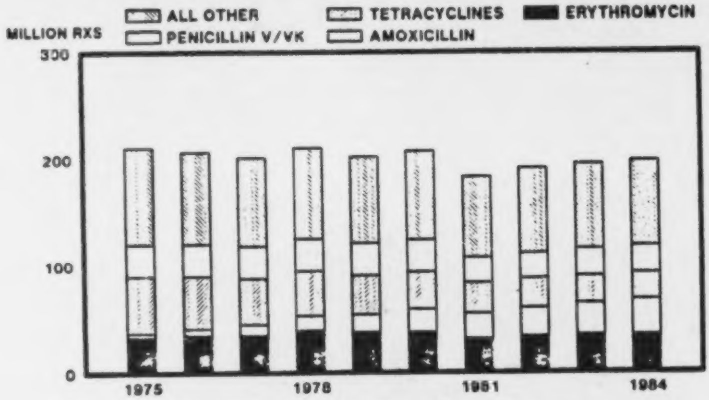

FIG. 4. Prescriptions for systemic antiinfectives from 1975 to 1984.

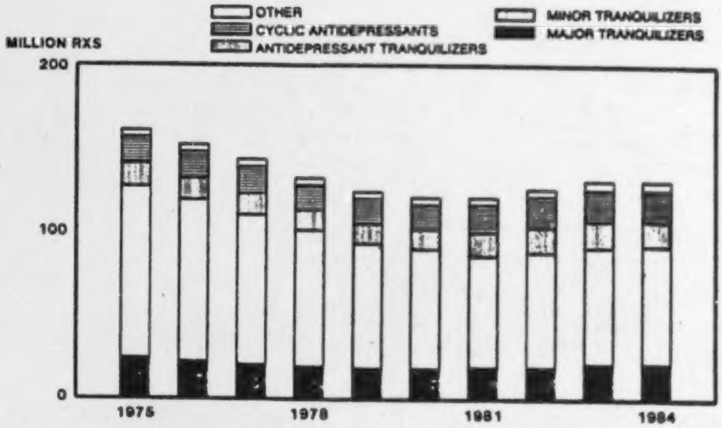

FIG. 5. Prescriptions for psychotherapeutic drugs from 1975 to 1984. The "other" category includes MAO inhibitors, lithium, and analeptics.

and the "potassium-sparing diuretics" category includes combination products that would more accurately be labeled as potassium-sparing/potassium-wasting diuretics.

Overall Drug Use

NPA data indicated that 1.53 billion prescriptions were dispensed from retail pharmacies (up 2% over 1983), at a consumer cost of $18.4 billion. The number of new prescriptions accounted for 49% of all prescriptions, while refills accounted for the remaining 51%. NDTI age demographics indicated that people aged 60 years and older accounted for the largest share of 1984 drug mentions (39%), while patients less than 20 years old accounted for the lowest share (17%). Sixty percent of total drug mentions were for female patients.

Figure 1 shows trends in overall drug use from 1971 to 1984. The number of total prescriptions dispensed in the United States increased by 15% from 1971 to 1984 with considerable variation during the intervening years. Total prescriptions peaked in 1973, decreased through 1979, and increased annually in the 1980s. The first year in which the number of prescriptions equalled the peak level of 1973 is 1984.

During this time period, both United States population size and prescription size (the average number of capsules, tablets, or other units in a prescription) were increasing. Figure 1 provides a more refined estimate of trends in outpatient drug exposure calculated by multiplying the number of prescriptions times average prescription size and dividing by population size. Data are presented as a change index, with 1971 as the baseline. Although prescriptions decreased for 6 years, population exposure decreased only in 1977, 1978, and 1979; increased in 1980 through 1982; and has been fairly constant for the past 2 years.

Major Therapeutic Classes and Drug Categories

Each of the 16 major therapeutic classes listed in Table 1 accounted for at least 2% of all prescriptions dispensed in 1984. To-

TABLE 1. Major Therapeutic Classes Representing at Least 2% of Total 1984 Prescriptions

Rank	Class	Number of Rxs (in Millions)	Percent of Total Rxs	Percent Change 1983–1984
1	Cardiovascular drugs	222	14	5
2	Systemic anti-infectives	196	13	0
3	Psychotherapeutic drugs	131	9	1
4	Analgesics	116	8	1
5	Diuretics	110	7	0
6	Hormones	84	5	2
7	Antiarthritics	73	5	3
8	Cough and cold preparations	57	4	0
9	Contraceptives	52	3	−2
10	Antispasmodics and GI/GU	51	3	4
11	Bronchial therapy	47	3	6
12	Nutrients and supplements	37	2	4
13	Ophthalmic preparations	37	2	4
14	Dermatologics	37	2	3
15	Diabetes therapy	32	2	11
16	Sedatives	31	2	1
	Total 16 classes	1,312	86	

Source: National Prescription Audit.

gether, these 16 classes represented 86% of total prescriptions. One half of all 1984 prescriptions were for one of the top five classes: cardiovascular drugs (222 million prescriptions); systemic anti-infectives (196 million prescriptions); psychotherapeutic drugs (131 million prescriptions, not including sedative hypnotics, which would add another 31 million prescriptions); analgesics (116 million prescriptions); and diuretics (110 million). Diuretics are used mainly to treat cardiovascular conditions, but the USC classification scheme treats them as a separate class. If we consider the two classes together, about 22% of all 1984 prescriptions were for diuretics or other cardiovascular therapy.

Cardiovascular Drugs and Diuretics

As shown in Table 2, four drug categories within the cardiovascular class each accounted for 2% or more of all prescriptions

TABLE 2. Top Cardiovascular and Diuretic Drug Categories in 1984

Drug Category[a]	Million Rxs	Percent of Total Rxs	Percent Female	Percent Aged 60+
Cardiovascular drugs	222	14	54	71
Beta blockers	61	4	55	55
Antihypertensives	56	4	60	66
Vasodilators	53	3	50	78
Digitalis	27	2	56	87
Diuretics	110	7	62	69
Potassium-sparing[b]	42	3	64	65
Thiazides	37	2	63	61
Other oral (e.g., furosemide[c])	30	2	59	79

Source: National Prescription Audit and National Disease and Therapeutic Index.

[a] Only those drug categories accounting for 2% or more of total Rxs are listed. Therefore, the class total may be greater than the sum of the listed categories.

[b] This category includes combination products in which only one of the ingredients is potassium sparing.

[c] 86% of prescriptions in this category were for furosemide.

TABLE 3. Top Anti-infective[a] Drug Categories in 1984

Drug Category[b]	Million Rxs	Percent of Total Rxs	Percent Female	Percent Aged 0–19	Percent Aged 60+
All anti-infectives[b]	196	13	56	38	22
Erythromycin	34	2	57	40	16
Amoxicillin	33	2	53	72	7
Tetracyclines	25	2	54	18	23
Penicillin V/VK	25	2	55	57	6

Source: National Prescription Audit and National Disease and Therapeutic Index.

[a] Excluding topical, ophthalmic, and otic anti-infectives.

[b] Only those drug categories accounting for 2% or more of total Rxs are listed. Therefore, the class total may be greater than the sum of the listed categories.

dispensed from retail pharmacies in 1984. Beta blockers, antihypertensives, vasodilators, and digitalis represented about 89% of total cardiovascular prescriptions. The diuretic class consists of only three categories, each of which represented at least 2% of total prescriptions.

NDTI data indicated that 71% of cardiovascular drug mentions were for people aged 60 or older. Not surprisingly, this is considerably higher than the 39% overall use for this age group. Women accounted for 54% of cardiovascular drug mentions. Patients on beta blockers tended to be younger than patients receiving drugs categorized as antihypertensives (who in turn were younger than those receiving vasodilators). Approximately 87% of digitalis use was in patients aged 60 or older, and other data suggest that digitalis is the most common drug exposure in the elderly.[2]

Diuretics are also used mainly in an older population, and "other diuretics" (mainly furosemide) are used in an older population than thiazides or potassium-sparing diuretics. The sex distribution is similar to overall drug use.

There has been a substantial increase in prescriptions for cardiovascular drugs over the last 10 years, from 132 million in 1975 to 222 million in 1984 (Fig. 2). Beta blockers have shown the most dramatic increase (from 9 million to 61 million). The increase in the "all other" category starting in 1981–82 is basically due to the introduction of calcium-channel blockers.

As shown in Figure 3, the use of diuretics has also increased over the past 10 years, from 78 million prescriptions in 1975 to 110 million prescriptions in 1984. Use of thiazide diuretics has remained fairly constant, while prescriptions for potassium-sparing diuretics have more than doubled. Prescriptions for "other" diuretics have increased by over 50%.

Systemic Anti-infectives

Systemic anti-infectives (excluding topical, ophthalmic, and otic products) were the second most commonly prescribed drug class in 1984. Four anti-infective categories individually accounted for 2% of total 1984 prescriptions: erythromycin, amoxicillin, tetracyclines, and penicillin V/VK. As shown in Table 3, amoxicillin has the highest percentage of use in patients under 20 years of age (72%), and tetracyclines have the lowest (18%).

Figure 4 indicates that the use of anti-infectives fluctuates little from year to year and has remained fairly stable over time (208 million prescriptions in 1975 and 196 million in 1984). The type of therapy has changed, with an eightfold increase in the use of amoxicillin, and a 53% decrease in the use of tetracyclines.

Cephalosporins (not shown in Figure 4) were the fifth most commonly dispensed

TABLE 4. Psychotherapeutic Drug Categories in 1984

Drug Category	Million Rxs	Percent of Total Rxs	Percent Female	Percent Aged 60+
All psychotherapeutics	131	9	64	32
Minor tranquilizers	71	5	65	35
Major tranquilizers	21	1	60	32
Cyclic antidepressants	19	1	68	31
Antidepressant tranquilizers	15	1	72	34
Other (MAO inhibitors, lithium, analeptics)	5	1	49	13

Source: National Prescription Audit and National Disease and Therapeutic Index.

anti-infective in 1984 with 23 million prescriptions. Their use increased by 147% over the 10-year period.

Psychotherapeutic Drugs

Table 4 provides data on the use of psychotherapeutic drugs in 1984. As a class, psychotherapeutic drugs are not often used in people less than 20 years old, and women account for almost two thirds of the use. Among the specific categories, the highest "percent female" was found for antidepressant tranquilizers (combination products or drugs like doxepin that are used for both anxiety and depression).

The largest difference is in the "other" category, which includes monoamine oxidase inhibitors, lithium, and analeptics. None of these drugs are commonly used by people in their sixties or older, and analeptics (drugs like Ritalin®) are used mainly in children (71% in people under 20). Males account for 75% of analeptic use.

Figure 5 displays trends in the number of prescriptions dispensed for psychotherapeutic drugs. Prescriptions for minor tranquilizers, the dominant category within the class, decreased from 103 million in 1975 to 67 million in 1981. Although this was the major factor in the 1975–1981 decrease in psychotherapeutic drug use, prescriptions for major tranquilizers (i.e., antipsychotic drugs) also decreased by roughly 20% during this period. Use of other psychotherapeutic drug categories remained relatively stable. Between 1981 and 1984, prescriptions for psychotherapeutic drugs increased by 9%, with the largest percentage increases in the "other" category (28%) and cyclic antidepressants and antidepressant tranquilizers (12% each).

Discussion

Both the type and extent of prescription drug use at any given point in time are related to many different factors such as population size and demographics, disease prevalence and detection, available drug therapies, and attitudes toward drug use. In general, increases in population size should lead to increases in prescription volume. Since Americans are becoming an older population,[7] we would expect an even greater increase in drug use than would be predicted based on population size alone, particularly for those drugs that are used for chronic conditions in the elderly. Data from the current study indicate that population size and prescription volume have both shown comparable increases from 1971 to 1984; however, annual changes in the rate of increase varied greatly until 1982. If one considers the increase in average prescription size during this period, outpatient drug exposure increased much more than would be predicted by population size. Prescriptions for cardiovascular agents and diuretics, drugs commonly used in the elderly, increased substantially from 1975 to 1984, while psychotherapeutics and anti-infectives, with lower geriatric use, decreased or remained stable.

The increase in use of cardiovascular drugs and diuretics may also be related to increased detection of hypertension. Sixty percent of adults with elevated blood pressure surveyed in 1976–1980 had been told by a physician that they had high blood pressure, as compared with 51% in 1971–1975 and 45% in 1960–1962. The proportion of hypertensive patients taking antihypertensive medication has shown a concomitant increase.[8]

The availability of new drug therapies may also have contributed to increased cardiovascular drug therapy. Twenty-seven of the 103 new chemical entities approved by the FDA from 1980 through 1984 were for treatment of cardiovascular conditions. Although the introduction of new or improved drug products may either expand the entire drug class or merely change the market share of individual products within the class, the former appears to be true in the case of cardiovascular therapy.

Availability of new drug products did not appear to have much influence on trends in outpatient anti-infective use. Although 32 new anti-infectives were approved by FDA from 1980 to 1984, most of these were for products that are used mainly in hospitals and thus are not reflected in the dispensed prescription data. Prescriptions for anti-infectives have remained fairly stable over the 10-year period, with annual fluctuations most likely related to variations in infectious disease rates from year to year.

Attitudes within both the general medical community and broader society can have a marked effect on drug use, particularly with drugs such as psychotropic agents where treatment decisions may be as strongly affected by attitudinal factors as by safety or efficacy considerations. The 1975–1981 decrease in prescriptions for psychotherapeutic drugs paralleled general concerns prevalent during that time about possible overprescribing and patient misuse of such drugs. Minor tranquilizers seemed to be the drugs of particular concern, and this category showed the sharpest decline in prescriptions.

The limitations of the current study should be noted. Ideally, drug use studies would provide estimates of the number of people exposed to a given drug or drug class. However, such studies are prohibitively expensive if one wishes to survey national utilization of all prescription drugs on an ongoing basis. Collecting data from physician and pharmacy panels is more economically feasible and can provide equally valid measures of drug use even though these measures may be less ideal than actual patient counts. All data presented here represent drugs "mentioned" during a physician–patient contact or drugs dispensed from retail pharmacies. We assume that differences in these measures (either in patient demographics or over time) reflect differences in the exposed population.

We speculate that increases in drug use, particularly use of cardiovascular drugs and diuretics, are related to the increasing proportion of elderly people in the United States population. Although the available data do support this, the differing characteristics of the NDTI and the NPA prevented us from age-adjusting the trend data to more directly evaluate the contribution of an aging population to changing prescription volume. The parameters of the present study also did not allow a direct assessment of the relationships between prescription volume and attitudes toward drug use or the availability of new drug therapies. The current data and common sense both suggest that these relationships do exist, but further explication will require more focused studies.

In summary, outpatient prescription drug use in 1984 consisted largely of the four therapeutic classes discussed above, which with analgesics accounted for one half of all dispensed prescriptions. As might be expected, patient age and sex differed with different drug classes and (generally to a lesser extent) with the specific types of drugs within each class. Drug use is not a static phenomenon but may change with population characteristics, disease prevalence and detection, new drug therapies, and general societal attitudes.

Acknowledgment

The assistance of Mary B. Forbes in data acquisition and analysis is gratefully acknowledged.

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Item 10

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Memorandum

To: Parties Interested in Clinical
Guidelines for the Elderly

SEP 30 1983

From: Acting Director
Office of New Drug Evaluation/HFN-100

Subject: Discussion Paper On Testing
of Drugs in the Elderly

Attached is a discussion paper developed within the FDA, on the testing of drugs in the elderly. It will be apparent that the discussion paper deals with general requirements for pharmacokinetic data as much as it does clinical requirements related to older patients.

Up to this time, we have had no formal comments from anyone outside FDA and we are now seeking comments from parties known to be interested in the problem. After evaluating these, we will develop a draft proposal through our usual guideline procedures, including a formal notification of availability.

Please direct comments to:

Robert Temple, M.D.
Acting Director, Office of New Drug Evaluation
Food and Drug Administration
Parklawn Building, Room 14B45
5600 Fishers Lane
Rockville, MD 20857

Robert Temple, M.D.

Attachment

SEP 30 1983

DISCUSSION PAPER ON THE TESTING OF DRUGS IN THE ELDERLY

DRAFT

Introduction:

There is a perception that drugs, even drugs likely to be used in the elderly, are not studied adequately in elderly patients and that as a consequence older patients are more likely than younger patients to suffer adverse reactions to drugs. It may be true that elderly patients are more likely to develop adverse reactions to drugs but, if true, the extent to which this is the result of age-related differences in drug response and insufficient clinical information about such changes, or is simply the result of an increased likelihood that the elderly will have concomitant diseases or will be using many drugs, is not really known. Most of those who have written about drugs in the elderly have found that the effect of age on the pharmacokinetics of drugs is the best established specifically age-related problem.

A recent survey of a dozen and recently approved pending new drug applications showed that older patients (over 65) are included in reasonably large numbers in studies of most drugs. Nonetheless, it is comparatively unusual for a sponsor to direct specific attention to the elderly to determine whether there ought to be specific labeling advice for them. It is therefore worthwhile to consider whether there are specific testing and analysis requirements that should be met by anyone planning to market a drug with potential usefulness in the elderly so that the clinician will be as aware as possible of special considerations involved in using the drug in older patients.

Although specific cases of age-related changes in pharmacokinetics or pharmacodynamics are recognized, it is not clear how common such changes are, nor, except for certain obvious situations, such as the increased half-life of renal-excreted drugs in elderly patients with diminished renal function, is it clear how to predict them. This is not solely a concern related to the elderly. Subpopulations with different pharmacokinetics can exist in any age group and detection of them has generally been difficult; a good pharmacokinetic evaluation of a drug will therefore contribute information allowing intelligent dose adjustment in patients of all ages.

The number of documented examples of age-related pharmacodynamic differences seems too small at this time to demand formal studies comparing younger and older patients with respect to their blood-level/response curves. The major impediment would be selection of an appropriate older population (well vs.

ill, specific decade of life, concomitant therapy or not). The approach suggested is therefore to use information collected from clinical trials that include older patients to search for possible pharmacodynamic differences.

Better information on using drugs in the elderly can be developed both from improvements in the general requirements for drug testing and from requirements related specifically to the older patient.

The general requirements are:

1. For any drug that has significant renal excretion of parent drug or active metabolites, there should be formal study of the effects of altered renal status on the drug's pharmacokinetics. Dosing information in product labeling should include instructions for the dosage adjustments needed for varying degrees of renal impairment.

   It would also be helpful to include in labeling for drugs needing such dosage adjustment a method for calculating the creatinine clearance from the serum creatinine, e.g.

   $$\text{male CCr} = \frac{\text{wt (kg)} \times (146 - \text{age})}{72 \times \text{Cr (mg/100 ml)}}$$

   $$\text{female CCr} = 0.9 \times \text{above}$$

   Such information is already commonly obtained for relatively toxic drugs; see, for example, current labeling for aminoglycoside antibiotics, a toxic group of drugs whose excretion is renal.

2. To implement a screening mechanism that will detect unanticipated pharmacokinetic problems in a setting that is reasonably comparable to clinical use.

The requirements specifically related to the elderly are:

1. To be certain elderly patients are not excluded from trials of drugs to which they will be exposed after a drug is marketed.

2. To analyze the safety and effectiveness results of clinical trials with attention specifically to the influence of patient age, as well as other characteristics that can be age-related (renal or hepatic status, muscle mass, concomitant therapy and concomitant disease). Depending on the findings arising from screening tests and analyses,

and on circumstances related to the specific drug, to carry out specific clinical trials needed to characterize the drug in the elderly.

In contemplating additional requirements related to study of drugs in the elderly, or to better evaluation of pharmacokinetics in general, the cost in time and money should be considered. It is apparent that, if planned at the outset of a drug's development, inclusion of elderly patients and analysis of results with respect to age are essentially cost-free. Exploration of pharmacokinetic questions such as the effects of renal impairment can be costly, but is plainly already a responsibility of a drug's sponsor, not a new requirement. Thus, the only significant new requirement and burden is the pharmacokinetic screening mechanism described below. Its benefits, however, appear to outweigh its costs.

Proposal:

The following requirements are therefore proposed as a means of assuring that clinicians will have adequate information to use drugs appropriately in the elderly. These include general requirements, i.e., improvements in drug evaluation that are applicable to many patients but that will have particularly value with respect to the elderly, and specific requirements, i.e. requirements related solely to the older population. The new requirements would be incorporated into the existing document called: "General Considerations for the Clinical Evaluation of Drugs".

I. General Requirements

A. Drugs that are excreted (parent drug or active metabolites) significantly through renal mechanisms should be studied to define the effects of altered renal function on their pharmacokinetics. Information should be developed for dosing instructions that provide appropriate adjustments for varying degrees of renal impairment. Labeling for such drugs should include a means of calculating creatinine clearance from the serum creatinine, adjusting for weight and age, because it is often difficult to obtain accurate direct measures of creatinine clearance without hospitalizing the patient for urine collections.

B. Drugs that are highly protein bound should be studied to determine factors that might influence degree of binding, such as total blood level, pH, etc. Ordinarily, much of this study can be done using in vitro methods.

C. Drugs in late Phase II and Phase III should be subjected to a "pharmacokinetic screen." A pharmacokinetic screen (not previously defined) is a simple means of determining whether a drug has pharmacokinetic properties that are likely to cause it to have unanticipated problems. It consists of a small number of blood level determinations during steady state dosing designed to display the variability in blood levels under defined conditions of dosing.

Depending on the half-life of the drug it might be sufficient to get a trough (pre-dose) value (probably suitable if the drug has a relatively long half-life) or alternatively, a trough and approximate peak value. If there are previous kinetic studies, the peak time can probably be estimated and one or two blood samples should be sufficient for an approximate peak level. If there are no prior studies, the peak could probably be approximated sufficiently by two or three measurements in the 1-3 hours post-dosing period. It might not be necessary to carry out these observations in every patient in Phase III but a sizable sample, including patients in all age, race, weight, and sex, groups, as well as patients with a variety of concomitant therapies and diseases, should be studied. Because a pharmacokinetic screen is relatively easy and inexpensive, at least if there is a suitable assay for the drug in body fluids, involving only one 1-4 blood level determinations per patient (a much less burdensome series of determinations than would be generated by the typical formal pharmacokinetic study) it is reasonable to cast as wide a net as possible in an effort to find atypical patients. Deviations could result from almost any factor that affected pharmacokinetics, including differences in metabolism and, of particular relevance to the elderly, differences in volume of distribution, hepatic metabolism, or renal excretion.

Studies of this kind are not intended to be similar in quality or precision to the typical formal pharmacokinetic study carried out on a new drug and they will not be able to detect small patient-to-patient differences. Concern that such a screen is not the best possible pharmacokinetic study should not be allowed to obscure the fact that what is most important is large differences, differences likely to be clinically important.

It is inherent in the idea of a "screen" that when the screen discovers something unusual, further studies would need to be done.

Thus, if a particular sub-population (e.g., people of a certain age, or those receiving specific other drugs or with other diseases) were found to have higher (or lower) blood levels than the rest an attempt to discover the reason for this would become necessary.

D. Drug-Disease and Drug-Drug Interactions

1. Specific Studies

Certain drug interactions are so common and so readily anticipated that it is almost always desirable to study them. These include:

a. Drugs known to have extensive protein binding can be expected to interact with specific concomitant therapies, specifically sulfonylureas, coumadin, phenytoin and certain NSAIDs, to cite a few examples. These interactions should be explored using in vitro or in vivo methods, as appropriate.

b. So many drugs affect serum levels of digoxin, which is widely used in the elderly and is potentially very toxic, that evaluation of this interaction is appropriate for virtually any drug.

c. Ophthalmic drugs (especially anti-glaucoma drugs) require compatibility testing with other topical ophthalmic drugs, which are frequently used in the elderly.

d. For drugs that undergo hepatic metabolism, the pharmacokinetic effects of known hepatic enzyme inducers should be studied.

2. Interaction Screen

If the drug is going to be used in conditions where specific diseases are particularly likely to be present (that is, other than the disease that is being treated with the test drug), an attempt should be made to include patients with the other diseases in the treatment population. The pharmacokinetic screen should be useful in determining whether the other diseases affect blood levels of the drug and clinical observations should permit detection of specific adverse effects associated with the other diseases. Similarly, with respect to other medications that are used concomitantly, the screen should help evaluate whether the other medications affect the kinetics of the test drug. In some cases, where a concomitant drug is used especially frequently, formal interaction studies should be carried out. For example, antianginal drugs of different pharmacologic classes (nitrate, beta-blocker, calcium antagonist) are so commonly combined that they should be subjected to formal studies of their combined effectiveness and tolerance.

It is also possible that the new drug will have an effect on the kinetics of other drugs. There is almost no limit to the number of studies that could be mounted to explore this question; therefore a second screening mechanism would be helpful. If Phase III clinical trials include patients who are on a variety of other drug therapies (held stable during introduction of the new agent), trough blood levels of the other drugs can be obtained prior to dosing with the new agent and again after the new agent has reached steady state. It should thus be possible to detect, with relatively little effort, major effects of the new drug on many concomitant medications. The principal limit to being able to do so will be the availability of good blood level measurements for the other agents. In general, drugs where blood levels are most critical are those for which blood level determinations are being developed.

II. Specific Requirements Related to the Elderly

A. Determination that a drug is likely to have significant use in the elderly

In many cases it is obvious that a drug will be widely used in the elderly because the diseases that it is intended to treat are characteristically diseases of aging, e.g. coronary artery disease, senile dementia, or peripheral vascular disease. In other cases it is not entirely clear what the age of ultimate population will be. A sponsor should determine through estimates of the disease prevalence by age or through examination of the age distribution for other drugs of a similar type (using the National Disease and Therapeutic Index, for example) whether his drug is likely to have significant use in the elderly.

B. Inclusion of Elderly Patients in Clinical Studies

Elderly patients should not be arbitrarily excluded from the patient population if a drug is likely to have significant use in the elderly. Sometimes, for example, patients over the age of 75 are excluded from clinical trials. There are reasons for doing this, principally, especially early in clinical studies, a desire to be sure that the patients' response to the drug will not be confounded by patients' underlying disease and fragility. Nonetheless, at least during Phase III, elderly patients should not be excluded. Ordinarily, elderly patients would be included in trials with other patients but in some cases, especially for drugs targeted to older patients or where differences in response by age are anticipated, trials could include only the elderly or, perhaps better, could specifically be designed to compare results in the older and younger patient groups.

C. Analysis of Adverse Effects and Effectiveness by Age

Adverse drug reactions and effectiveness should be analyzed taking age into account. It is possible to do a variety of analyses of effectiveness or adverse effects looking for relationship to dose, race, underlying disease, and age. This should be done both for individual studies and as an overall analysis. There would have to be a fairly substantial difference in effectiveness or adverse reaction rates by age before a difference could be detected; that is less a problem than it might seem, as unless the difference is rather large it is probably not of major importance.

This kind of analysis might need to be followed up by formal dose-response studies, or if possible, blood level-response studies, specifically in the elderly; such studies might be done earlier in the drug's evaluation if the drug was particularly directed at the elderly or if it was a member of a class where pharmacodynamic differences with age might be expected, such as benzodiazepines.

Alternative

There are other ways to approach the question of drugs in the elderly.

Dr. Crooks of Dundee (Scotland), in a paper prepared for the Committee on Safety of Medicines, first discussed the kinds of differences that might exist between the elderly and younger people and proposed the following approach:

> He identified drugs liable to produce special problems in the elderly as (1) drugs with indications for use that are commonly found in the elderly, (2) drugs with a low therapeutic ratio if associated with one or more of the following: (a) drugs primarily eliminated by renal excretion (or with biologically active metabolites excreted in the urine), (b) drugs with a high liver extraction ratio, (c) drugs that act directly on the central nervous system and (d) drugs that have an effect likely to be modified by the impairment of homoeostatic mechanisms commonly found in the elderly.

He proposed that for drugs meeting those criteria a product license would require the following addit onal studies:

(1) single dose pharamcokinetic studies in healthy, elderly patients (greater than 70 years old) and where the single dose data are marketedly different from the young, multiple dose studies as well.

(2) pharmacodynamic studies in elderly patients with the condition for which the drug is indicated.

(3) safety and effectiveness of the drug must be established in the elderly under clinical trial conditions using the dosing regimen considered to be appropriate for the elderly on the basis of the pharmacokinetic and where available pharmacodynamic data.

Although this approach is in many ways similar to our proposal, I believe it has a significant problem:

> The first two studies would necessarily be carried out in "healthy elderly" patients and in a rather small number of them. As the elderly are almost surely quite diverse with respect to differences from younger patients, many potential problems seem likely to be missed. Nonetheless, the recommended studies are comparatively easy to carry out and the approach is in some ways less demanding. Commentators should consider it in their responses.

Item 11

GUIDELINES FOR STUDYING DRUGS IN THE ELDERLY

By

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Presented at The Drug Information Association Workshop on Geriatric Drug Use, Washington, D.C., February 28, 1984

Several months ago we made available a "discussion paper" on the testing of drugs in the elderly - it was in essence a pre-proposed guideline. The paper offered a general overall approach to the evaluation of the effects of any drug in the elderly and was based on several premises:

1. The problems of drugs in the elderly are only in part, perhaps small part, the result of age *per se*. They are also the result of illnesses or influences that can occur at any age, but may be more common in the elderly.

2. Much of the information needed to use drugs safely in the elderly can be derived both from the elderly and from younger patients, such as:

    - how the drug is metabolized and excreted and therefore what derangements might influence metabolism or excretion.

    - the relationship of blood levels of drug to pharmacologic effect. This may be altered in the elderly but this cannot be learned until the non-elderly are well-studied.

    - the presence of drug-drug interactions, either pharmacokinetic or pharmacodynamic.

    - the presence of drug-disease interaction.

3. The elderly are so heterogenous with respect to physiologic processes, other drug use, and concomitant illness that their specific problems can best be identified if a broad range of elderly patients are included in trials and multi-variate techniques are used

to distinguish the influence of age per se and the influence of characteristics that tend to occur more frequently with greater age but are important no matter when they occur.

This is not a unique problem. While it is still debated, and there is evidence on both sides, there has been a question as to whether obesity is an independent, cardiovascular risk, or whether the elevated blood pressure, blood sugar, and cholesterol associated with obesity (or perhaps obesity - provoking diet) are the only risk factors. To give the best possible advice you need to know the answer.

4. We are usually not wise enough in advance to know where to look for trouble. Therefore, in addition to looking at identified trouble areas, we need to set in place mechanisms to find the unexpected.

5. There is no insurmountable obstacle to including the elderly, in fairly sizable numbers, in clinical trials. We know this because patients in their 60s and 70s have regularly been included in evaluations of drugs in recent years (as a mini-survey of recent NDAs showed). Beyond the 70s it may become difficult as increasing difficulties can be expected in such mundane matters as reaching the clinic, assuring compliance with medications, obtaining informed consent, etc. You will note I have given no age at which people become "elderly". In part that is because no one is likely to agree, and in part because the idea that people switch categories all at once is naive. Somewhere between 60 and 80 it happens to us all - NDAs should include a good representation of patients in this age range.

The solution that arose from these premises is somewhat complicated, with several components, reflecting an attempt to study those areas that we know are likely to cause problems in the elderly, study the basic properties of drugs better than we have in the past, and examine the rich data base of an NDA as well as possible to discover new information.

We did not think it was enough simply to say: if the drug is to be used in the elderly carry out clinical trials and a pharmacokinetic study in old people. It seemed almost inevitable that such studies would be carried out in a relatively healthy elderly population, with special care devoted to dose selection, and would show little except the usual response. These studies may be useful sometimes but are not sufficient. Accepting them as sufficient would, I think, be deceiving ourselves.

We therefore proposed the following set of requirements, some related specifically to the elderly, others to obtaining general information that will be useful to all age groups, including the elderly.

I. Better Study of Factors Known to Alter Pharmacokinetics

It appears at this time that a substantial fraction of the drug problems in the elderly has to do with alterations in the pharmacokinetics of drugs. It is not well enough recognized that changes in creatinine clearance are very common in the elderly and accurate clearances are hard to obtain, as they require 24 hr. urine collections. There is a simple formula developed by Cockcroft and Gault:

$$\text{male CCr} = \frac{\text{wt (kg)} \times (140\text{-age})}{72 \times \text{Cr (mg/100 ml)}}$$

$$\text{female CCr} = 0.9 \times \text{above}$$

For most purposes the formula gives an estimate superior to any but the most meticulous measurements. Marc Reidenberg wrote to tell me of his recent study in hospitalized patients comparing the estimate using the above equation and actual CCr measurements. Whenever there was a meaningful difference between the estimate and the measurement, repeat of the measurement gave a value closer to the calculated value than to the previous measured value.

In addition to knowing CCr, we must know how the kinetics of the drug are affected by changes in renal function. Therefore, any drug excreted (parent drug or active metabolites) through renal mechanisms should have formal study of the effect of altered renal function or its pharmacokinetics. Labeling for such drugs should portray this relationship and include the Cockcroft and Gault equation above, or provide a nomogram equivalent. This is clearly possible, as it already is done for the aminoglycosides, a renally excreted class of drugs with a very narrow therapeutic ratio.

The proposal suggested routine study of the influence of protein binding on kinetics, but several comments cast doubt on the usefulness of this.

The proposal did not mention purely biopharmaceutic matters but there is growing interest in such factors as pH-dependence of dosage forms and effects of delayed gastric emptying. The elderly are more likely to be hypochlorhydric and to have delayed emptying.

The proposal did not consider relating kinetics to hepatic function such as might be assessed by an aminopyrine test, but Dr. Greenblatt's discussion suggests potential usefulness of such an effort. The problem, obviously, is that relatively few physicians utilize an aminopyrine test as part of their clinical dose-selection procedures, so that identifying a relationship might be of little practical value.

II. A Screen for Unknown/Unsuspected Pharmacokinetic Effects

The proposal includes a "pharmacokinetic screen", a procedure involving obtaining a small number of blood samples during steady state dosing from many patients to look for unexpectedly high or low blood levels.

At present pharmacokinetic studies are carried out principally in small numbers of normal males. Only if obvious problems develop are searches made in other populations, except that kinetics in patients with abnormal renal function are fairly commonly studied and certain specific drug interaction studies (e.g., effects on digoxin or coumadin) are increasingly common.

If there is a suitable blood level assay, preferably one not too dependent on perfect handling of samples, blood levels obtained during clinical trials should be able to detect major deviations from what is expected. Once detected, the reasons for the deviation must be sought among the usual factors, such as:

- demographic characteristics (age, race, sex)

- effects of other disease (hepatic function, CHF)
- effects of other drugs (cimetidine, barbiturates)

- population differences in metabolism (isoniazid, procaine amide, encainide)

- unrecognized peculiar kinetics (non-linearity)

The proposal suggested that several blood levels would be needed to define approximate peak and trough levels. One comment, from Dr. Reidenberg, who was concerned that the suggestion was needlessly burdensome, suggested that trough levels alone would suffice, for several reasons:

1. Trough and peak are related,

2. The usual clinical correlations of drug effect are with trough levels,

3. Peak will be hard to find and requires arbitrary choices.

Obviously, it would be substantially easier to obtain trough levels only. Timing would be less critical and fewer samples needed. This bears further discussion.

Dr. Reidenberg also suggested that the screen could be omitted if certain conditions obtained: e.g., if a drug was eliminated wholly as the unmetabolized parent compound by the kidneys, the renal work-up might suffice. Or, if a drug had an easily measured, rapid response clearly related to dose (some antihypertensive agents) you might well know well enough how to use it from the kinds of studies now carried out. These points too bear further discussion.

Let me emphasize that a "screen" is a hypothesis-generating device, not usually able to provide a definitive answer. If outliers are found, their characteristics (age, race, disease, other drugs, obesity, etc.) need to be examined to seek an explanation and further studies in them could be needed. It would also be important to determine whether the observed drug responses in outliers (effects, ADRs) were different, as it is the clinical importance of a pharmacokinetic alteration that is our real concern.

III. Studies of Pharmacokinetic Interactions

There are a few formal studies of drug-drug interaction that probably should be part of any drug evaluation (e.g., effects on digoxin serum levels) and some studies are suggested by the way drugs will be used (e.g. antianginal and anti-CHF drugs will be used together and should be studied together), but a screening mechanism seems useful here, again concentrating on pharmacokinetic interactions first. Proposed is a simple comparison of trough, steady-state blood levels before and after introduction of the new drug. Obviously, this can be done most readily where the institution is already capable of monitoring blood levels of a particular drug and setting up many new assays would be prohibitively costly. It is often, of course, the drugs whose levels are most critical (phenytoin, quinidine, digoxin, etc.) that hospitals choose to measure, so that the screen would be targeted to agents of major interest.

IV. Special Age-Related Requirements

As noted, the above requirements would greatly enhance knowledge of drugs pertinent to the elderly but are pertinent to all patients.

Several additional requirements are needed:

1. Drugs should be explicitly described with respect to how likely their use in the elderly is. This may be self-evident from the target population (CHF and angina, e.g., obviously are common in older patients) but, if not, can be derived from sources such as Medicaid or the National Disease and Therapeutic Index.

2. Elderly patients should be included in clinical trials. They usually are, at present, but sometimes there are arbitrary age limits (e.g., patients over 75) that seem of doubtful necessity. Caution, especially early, is understandable, but by Phase III, older patients should be included.

   The proposal does not call for routine specific clinical studies in the elderly but suggests that the elderly be included in other trials, as they appear. Clearly, however, for drugs very specifically targeted to the elderly or where differences in response by age might be expected (e.g., sedatives), trials in the elderly could be carried out or, even better, response in old and young could be specifically compared. The previous discussion by Dr. Greenblatt suggests that it would be appropriate to carry out pharmacokinetic studies of any high clearance oxidized drug in the elderly.

3. Analysis of adverse effects and effectiveness by age.

   I am impressed that we do not sufficiently use the mass of data in an NDA to look for factors that affect response, factors such as age, race, dose (in mg/kg), other diseases, other drugs, obesity, or blood level. I recognize that cross-study pooling of data for such an analysis is risky but there is no possibility of gaining these insights in any other way, unless someone is smart enough to suspect such a relationship. Certainly, suspected relationships should be pursued, but sifting the data for surprises is also of value.

It should be obvious that we are proposing no "cookbook", but rather an approach. Some commentators preferred an alternative suggested by Crooks and possibly being used in England. The alternative is to identify drugs likely to create problems in the elderly:

1. Drugs intended for indications commonly found in the elderly.
2. Drugs with low therapeutic ratio and either:
    a. renally excreted
    b. having a high liver extraction ratio,
    c. acting on the CNS, or
    d. having an effect likely to be modified by the impairment of homeostatic mechanisms commonly found in the elderly.

For these, three studies would be needed:

1. Single-dose pharmacokinetic studies in healthy older patients (70 years old).
2. Pharmacodynamic studies in elderly patients with the disease to be treated.
3. Establishment of safety, and effectiveness in the elderly using trial conditions suggested by the above results.

The proposal has merit and may represent a reasonable minimum effort. Its problem, I think, is that it focuses on age alone. I do not believe, and more important, the gerontologists who write about drugs and the elderly do not indicate, that the specific effect of age is the biggest problem. The biggest problem is the effect of age in causing a variety of diseases and system impairment, and need for other drugs, resulting in a wide range of interactions. The above studies, carried out in a fairly healthy older population will tell about the specific effects of age but will leave the elderly unguarded against problems that arise, not from age itself, but from age-related impairments of excretion, need for other therapy, and concomitant illness. I believe the broader approach proposed, refined by comments from within and outside FDA, while perhaps more difficult to implement, has greater promise.

The next step, after reviewing all comments, and perhaps convincing groups to discuss specific issues, will be a proposed guideline, probably presented as a series of specific amendments to our General Guidelines. I hope people here and anyone else interested will comment as soon as possible so that the proposed guideline is the best possible document. The most effective comments are those that include specific alternatives.

Item 12

FDA GUIDELINES FOR CLINICAL TESTING OF DRUGS IN THE ELDERLY

By

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Presented at the DIA Workshop on Geriatric Drug Testing and Development - Practical Applications, April 2, 1985, Bethesda, Maryland

Current Status

In September 30, 1983 we made available a "Discussion Paper on Testing of Drugs in the Elderly, a preliminary statement of what we intended eventually to propose as a formal guideline. The response to the discussion paper was gratifying and a host of serious comments, criticisms, and suggested alternatives were sent to us. The most recent evaluation was a workshop sponsored jointly by ASCPT and FDA on September 13 and 14, 1984, from which a number of specific recommendations emanated. At present, I am reviewing all comments and hope to have a proposed guideline out by the end of summer. Work on the many other guidelines promised as part of the new NDA regulations has set back my schedule to some extent.

You may recall that the initial discussion paper emphasized several major principles.

1. Although the elderly (patients over 65) are at present often, even usually, included in drug studies, there rarely is specific attention in an NDA directed at differences in pharmacokinetic and pharmacodynamic response between the elderly and younger patients.

2. Many of the potential differences between older and younger patients are not the result of age per se. Rather, they result from factors that are more common in the elderly, but can occur at any age, such as changes in renal or hepatic function, use of concomitant medication, or presence of multiple diseases.

3. Because the potential interactions of age, metabolic changes, other drugs, and other diseases are exceedingly complex, single studies of one factor at a time, while important, cannot be adequate and the larger data base available in clinical trials ought to be utilized.

From these principles flowed several proposals:

1. The elderly should be included in trials of drugs to which they will be exposed.

2. Clinical trials must be analyzed to examine the influence of age, as well as other characteristics, on effectiveness and safety outcomes. In addition to age, factors related to age, such as renal or hepatic status, lean body weight, concomitant therapy or disease, should also be analyzed.

3. Any drug with significant renal excretion of parent drug or active metabolites should have formal study of the effects of altered renal status on kinetics.

4. There should be two screening mechanisms to examine:

   a. the effect of a new drug on serum levels of drugs the patient is already receiving (the interaction screen), and

   b. the variability, and factors linked to such variability, of serum levels (or, more broadly, the pharmarcokinetics) of the new drug - this is the so-called pharmacokinetic screen.

ASCPT Workshop

The September 1984 ASCPT Workshop engendered spirited discussion, organized in four workshops:

Formal Pharmacokinetics
Pharmacokinetic Screen
Pharmacodynamics
Clinical Trials

The major conclusions of the workshops were as follows:

A. Formal Pharmacokinetics

A systematic evaluation of pharmacokinetics should proceed from healthy volunteers to patients with diseases of the organs of disposition and to the intended patient population. Drugs with significant renal excretion should be studied to define the effects of altered renal function on excretion; this will inevitably identify age-related changes as renal function declines with age. This information is needed to choose dosage regimens for studies in the elderly; in addition, the possibility that the elderly are more sensitive needs to be recognized.

The panel felt that before enrolling elderly patients in effectiveness trials, the clinical pharmacology in a comparably aged group of healthy volunteers should be studied. I should note that Marc Reidenberg disagrees. He believes you can do such studies in elderly with the disease. While an effect of decreased renal function is anticipated in the elderly, changes beyond that expected from renal function need analysis, perhaps further study.

B. Pharmacodynamic Considerations

The possibility of disease or age-related changes in pharmacodynamic response must be considered but must be interpreted and looked for in light of identified kinetic changes. Inclusion of older patients in regular phase 2/3 type trials should generally be sufficient to identify problems and ad hoc pharmacodynamic studies used as appropriate. If they are needed, non-invasive measures should be emphasized. Evaluation of CNS drugs may be especially important because of poor correlation of plasma concentration and response and potential drug-drug interactions.

C. Clinical Trials

Since most drugs are used extensively in the geriatric age group, it is desirable, whenever possible, to include a reasonable sample of patients over 65 in phase 2/3 trials. Age per se should not be an exclusion. Obviously, in the case of drugs intended for the elderly (Alzheimer's Disease, Parkinson's Disease, glaucoma, or developed osteoporosis) older patients should represent the majority.

Depending on early kinetic or pharmacodynamic data, trials specifically directed at examining age-related differences in drug disposition or response may be needed.

In trials involving elderly (and others) information potentially related to response should be gathered, such as nutritional status, alcohol intake, smoking habits, renal function, activity level, mental status, and concomitant illness and drug therapy.

D. Pharmacokinetic Screen

For any drug and any patient population, patient or disease factors, including other therapy, that ought to substantially alter dosage instructions (dose, interval between doses) should be well-defined. The elderly are particularly in need of attention to dose because they have many of the factors that are likely to alter the dose-response relationship, including altered excretion or metabolism, multiple drugs, multiple diseases, etc. Defining what factors influence the kinetics of a drug provides data applicable to all patients, not only elderly ones.

While understanding of the influence of single factors (renal disease, another drug) is critical it is important to know the extent to which measurable characteristics can account for the observed variability in blood concentrations and the extent to which there are unexplained inter-individual variations. Kinetic studies in normal volunteers or formal studies in small numbers of patients, cannot satisfy this need. A pharmacokinetic screen, defined as an observational study of pharmacokinetics on patients enrolled in a phase 3 study, could be an attractive means of gaining information" on both aspects (predictable and unpredictable variability) of pharmacokinetics "if the applicability and value of such a screen to the new drug evaluation process can be demonstrated. Its purpose would be to systematically confirm and extend earlier information on population pharmacokinetics and to identify unanticipated problems that may have a pharmacokinetic basis, after taking into account reasonable *a priori* factors."

As to how to do the screen, the panel noted that several methods were possible. The simplest would be one trough level per patient. The other extreme would require several samples per patient and greater data accuracy (timing, etc.). The methodological issue interacts with practical considerations (Can timing of sampling and dosing be

> measured precisely enough to make the more compulsive study worthwhile and will sample preservation and transport be adequate) and the evaluation of ultimate usefulness: Will such studies "reveal therapeutically significant information not available from the current new drug evaluation process [and] if so, do the more elaborate designs produce sufficiently more precise and complete information...to justify their added difficulty?"
>
> The panel made no definitive recommendation on methodology but called for evaluation of the practical feasibility of various methods in a prospective fashion to evaluate possible implementation in a guideline. They urged a cooperative (FDA, industry, academic) venture to carry out and evaluate such a study. Even if feasible, the screen would complement, not replace current approaches. The Panel felt the results of a screen should not influence FDA decisions about approval but should be used to enhance therapeutic use of the drug. The screening process cannot create new untoward clinical events, it only adds blood level measures to the studies already taking place. Rather than endangering drug approval "it may provide satisfactory explanations of [untoward] events, thereby mitigating the extent to which they might have placed drug approval in jeopardy."

In addition to the Panels, a draft proposal for an FDA guideline was prepared. Much of it restates the above, a bit tersely for my taste, but there are a few sections that are controversial, especially the first sentence, which states:

> "Drugs expected to be widely used in the elderly (65 years of age or older) and (a) affect biologic homeostatic mechanisms which may be deficient in the elderly, (b) act in the central nervous system or (c) have a low therapeutic to safety ratio and 1) are excreted largely by the kidney, 2) are subject to large first pass effect, 3) are metabolized by oxidative mechanisms, or 4) generate significant metabolites require special attention in this population."

One participant in the workshop objected to this, saying that any drug widely used in the elderly deserves proper pharmacokinetic evaluation and that a large first pass effect and oxidative metabolism should not be singled out as factors requiring special attention, other factors being equally important.

The answer, I think, is pretty clear, and I don't believe the proposed paragraph meant to do anything but direct special attention to higher risk situations. A good pharmacokinetic evaluation is needed for any drug. After basic studies in normals are available, I believe a screening mechanism would, if implemented, diminish the need for many routine kinetic studies, and would instead guide the drug evaluators toward those studies really needed. In the absence of a screen it is probably necessary to carry out a kinetic study in the elderly for any drug to be used in the elderly, and probably to study kinetics in patients, which is not current practice.

As I indicated, I hope to complete a proposed guideline by the end of summer. It will not require a pharmacokinetic screen but will certainly include the concept as a discussion point and perhaps as an optional alternative to specific studies.

A screening approach is still by far the best, and perhaps the only, way to look at the multiplicity of factors that might affect pharmacokinetics and, most important, to discover early, an important factor that is unexpected. Until we screen we will have to look at factors one at a time, such as:

- effects of other drugs
- effect of renal function
- effect of age
- effect of hepatic function, etc.

But you quickly reach a practical limit to the number of specific studies that can be carried out. Someday we will, I am sure, allow as many as possible of the thousand or so drug exposures in an NDA to help define the way the larger population will handle a drug, instead of relying on 20-40 normal volunteers, as we do now. Once we have pinned down the pharmacokinetic variables we can start to use the same data base to look for ideosyncratic or systematic differences in pharmacodynamic responses.

The Clinical Investigation of Drugs for Use by the Elderly

Item 13

by

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It has been three years since we offered to the community a Discussion Paper on Testing of Drugs in the Elderly. The paper was intended to be the opening phase in the development of a guideline for the study of drugs in the elderly and clearly came at a favorable time. The response to it has been enthusiastic, reflecting general appreciation that the use of drugs in older patients needs more attention, as well as growing recognition of the diversity in response to drugs that can arise from a variety of causes. There has been a gratifyingly large amount of discussion on what the content of such a guideline should be, and a quite general agreement among academics and the drug industry that the evaluation of drugs in the elderly can be, and should be, improved. There is more than mere enthusiasm; it is apparent from recent NDA submissions to us, and from scanning the literature, that there has been an explosive increase in the numbers of studies and analyses attempting to relate drug responses to age and other possible demographic or pathophysiologic influences. In a recent NDA for encainide, an anti-arrhythmic agent, for example, there are:

1. A specific comparison of the pharmacokinetics in young (21-39) and older (over 65) healthy normal individuals.
2. Specific studies of the effects of abnormal renal and hepatic function on pharmacokinetics.
3. A specific examination of hemodynamic effects in younger and older patients with relatively severe cardiac disease.
4. A systematic search of the clinical data base for drug-drug interactions as well as specific studies directed at the pharmacokinetic effects of cimetidine on the antiarrhythmic agent and of the new agent on digoxin.
5. Elucidation of a complex metabolic scheme including two active metabolites and two different metabolic subpopulations linked to debrisoquin metabolizer status.

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The initial NDA data base included over 1,000 patients, with more than 500 over age 60, more than 300 over age 65, and about 150 over age 70. The final data base is about double that. The exposure of the older population is thus obviously very substantial, but that was not unusual in the past: What is new is the overall pharmacokinetic sophistication and the attempt to examine specific factors that could alter response to the drug.

When we examined a sample of NDAs a number of years ago, we also found that the elderly were included in trials in good numbers. Indeed, it would be difficult to carry out trials in most therapeutic areas without doing so. But the specific clinical pharmacologic attention to older patients, and to other patient subsets, is new, and very important.

While the promised proposed guideline for study of drugs in the elderly has not yet emerged, principally because other guideline-related activity has occupied me, drug manufacturers have, based on the discussion paper, subsequent workshops, and the growing interest in the subject, even without a formal guideline, begun to obtain the data needed to use drugs safely and effectively in older patients. One further event that should stimulate further attention to such data was the publication in September 1985 of a proposed Guideline for the Format and Content of the Clinical Section of a New Drug Application. This guideline does not, for the most part, demand specific data -- it simply tells where to put the data available and how to display and analyze it -- but it does give guidance as to our expectations. Moreover, it asks specifically for analysis of clinical data to look for age-related (as well as other subset-related) effects on safety or effectiveness, i.e., differential responses to the drug in particular segments of the treated population. Most applications now reaching my office include an attempt to discover such subset differences.

Change, described in more detail by others at this workshop, is thus already occurring; while I might have wished to finish it earlier, the formal guideline proposal should emerge early in 1987. Like most guidelines, it will reflect the best practices already in place, rather than create something really new. The extensive discussions we have had since the discussion paper, the greater experience we are obtaining in carrying out studies in older patients, and, more extensive recent experience in obtaining population pharmacokinetic (blood level) data in phase 3 trials, will lead to a better, more useful guideline.

The general principles underlying a guideline for study of drugs in the elderly set forth in the discussion paper still seem sound, and I would like to review them:

1. Age-related differences in response to drugs can arise from pharmacokinetic differences, i.e., differences in the way a drug is absorbed, excreted, metabolized, or distributed, or from pharmacodynamic differences, i.e., differences in the response to a given blood concentration of the drug. Age-associated pharmacokinetic or pharmacodynamic differences could result from age itself or from conditions that are more common in the elderly but do not represent an effect of age per se.

2. For a number of practical and theoretical reasons, studies to evaluate possible differences in the elderly should focus initial attention on assessment of pharmacokinetic differences between age groups.

   First, such differences are known to occur, and are much more frequent than documented pharmacodynamic differences. Most problems with drugs in the elderly identified to date result from pharmacokinetic differences related to age itself or to age-associated conditions such as renal impairment, congestive heart failure, or multiple drug therapy.

   Second, they are relatively easy to assess. Once a good assay for a drug and its metabolites is developed, and nowadays it almost always is available early in development, techniques exist for readily assessing age-related or other influence-related effects. Moreover, aside from the recognized value of formal pharmacokinetic studies, there is good reason to believe that population pharmacokinetic evaluation in phase 3 populations is practical; i.e., it will be possible by obtaining a small number of blood level determinations in many phase 3 patients to allow detection of markedly atypical pharmacokinetic behavior in individuals, such as that resulting from the metabolizer subtypes seen with encainide, and more subtle differences in pharmacokinetics in population subsets, such as age, sex, race, underlying disease, or concomitant therapy subsets.

I would contrast the relative ease of pharmacokinetic analysis with the difficulty of developing precise relationships of dose or, better, blood level, to response. Surprisingly few drug applications we see provide excellent dose response information.

A third reason for emphasizing pharmacokinetics is that it must be evaluated first to allow assessment of pharmacodynamic differences. Assessing pharmacodynamic differences between groups is possible only when groups are well-matched for blood concentrations. Enough data must therefore be available to permit the attainment of comparable blood concentrations in the subsets to be compared.

3. The number of documented age-related pharmacodynamic differences is so small that formal studies to seek such differences between the blood level/response curves of younger and older patients are not warranted, in my view, unless they are suspected for some reason or appear particularly important, eg., because of a low therapeutic index. The observations made during clinical trials that include both younger and older patients, however, if properly analyzed and particularly if accompanied by blood level data for each patient, should allow detection of important pharmacodynamic differences related to age or other influences. This is simply a matter of using data already available. I should note that this principle is somewhat controversial; the ASCPT Workshop was more enthusiastic about carrying out formal pharmacodynamic studies in the elderly.

4. Age is not the only subset characteristic of interest; in fact, most problems seemingly related to age are not related to age itself but to conditions that are more common in the elderly but that can occur in patients of all ages, such as diminished renal or cardiac function, other concomitant illness, and concomitant treatment. What is needed is an approach that will detect, better than is done at present, all of the patient characteristics that influence response to therapy. Even if age itself is not a particularly important factor, the conditions that are common in the elderly are likely to be very important. Understanding their influence will therefore greatly enhance our ability to treat older patients with appropriate doses.

With these principles in mind, the critical features of a proper evaluation of a new drug with respect to the elderly are these:

1. Include the elderly in clinical trials if they will be exposed to the new drug after it is marketed.

   Whether elderly patients will be exposed will often be obvious, as many drugs are intended for diseases common in the elderly. If doubt exists, the use pattern of drugs with similar claims can be determined from such sources as the National Disease and Therapeutic Index.

   Although it is reasonable and necessary to exclude patients too infirm to participate in clinical trials, patients unable to provide meaningful informed consent, and patients with too much complicating illness, rigid age cut-offs and routine exclusion of all patients with concomitant illness and medication is unnecessary and counter-productive. It tends merely to delay discovery of important problems and interactions; it cannot prevent them.

   Whether it is preferable to carry out specific trials in older patients or to include a range of ages in studies can be debated. In all probability, both approaches have merit, but I have a bias in favor of the latter as the usual procedure. What we want to see is whether older patients respond differently from other patients. If older patients are studied in a separate trial, there will be no younger patients available for direct within study comparison; the only comparison will be across studies, i.e., comparing patients in one study with patients in another. Since conditions in different studies cannot be presumed similar, such comparisons are very treacherous.

   Nonetheless, where drugs are specifically targeted to the elderly, where drugs have properties that seem to pose particular problems for persons with impaired homeostatic mechanisms (e.g., a drug that has a negative inotropic effect or causes orthostatic hypotension), or where the drug has important CNS activity, specific trials in the elderly, or in particular groups of the elderly who may be at special risk, should be conducted. It may be possible to obtain the best of both approaches by stratifying patients in controlled trials by age; this allows for the elderly to be studied specifically, yet in a way that allows comparison with other age groups in the same study.

It does not seem reasonable to propose at this time the routine duplication of clinical pharmacology studies (except perhaps for pharmacokinetic studies) in young and old patients to look for differences in response because there are too few examples of pharmacodynamic differences due solely to age. Differences of clinical importance should be detectable in clinical trials.

2. Analyze the influence of age on adverse events and effectiveness.

Although, contrary to what is sometimes said, older patients have been included in clinical trials in the past, it was uncommon to examine trial experience to see whether age affected response. This has changed, and it is now common to see such analyses, as well as analyses of the relationship of response to other relevant patient characteristics, such as sex, race, underlying disease, concomitant treatment, and dose. Unless differences of this kind are large, they can be detected only in quite large single studies, so that it is usually necessary to pool data from many trials to make such an assessment. Unfortunately, such pooling will itself tend to obscure small differences because the trials themselves differ. Of course, it is only differences of substantial size that would tend to need alterations in therapy, so that the approach is still useful.

Any attempt to relate benefit or adverse effect to factors such as age will be greatly improved by good pharmacokinetic data. Suppose, for example, that older patients are found to have more adverse effects. If older patients also show higher blood levels of drug for any given dose, we would suspect that the observed differences are related to different metabolism or excretion and simple dose adjustment should be able to solve the problem. If, on the other hand, older patients have blood levels similar to those in younger people but still have more side effects, the problem is more difficult; older patients may need to sacrifice effectiveness to gain tolerability or at worst, the drug may not be useful in the elderly.

If a true pharmacodynamic difference is suggested by the overall analysis of data, formal dose-response or blood-level response studies in older patients will be needed.

3. Seek and transmit via labeling better information on all of the factors that affect pharmacokinetics of the drug, including age.

   a. Drugs that are excreted (parent drug or active metabolites) significantly through renal mechanisms should be studied to define the effects of altered renal function on their pharmacokinetics. Dosing instructions appropriate for varying degrees of renal impairment should be developed. Labeling for such drugs should include a means of calculating a creatinine clearance from the serum creatinine and age because it is often difficult to obtain accurate measured creatinine clearance outside (or even in) the hospital setting.

      While altered renal function is a possible problem at any age, it is a major cause of drug toxicity in older patients.

   b. Drugs that are subject to significant hepatic metabolism, especially those with large first pass effects, with metabolism by oxidative mechanisms, or with active metabolites, require particular attention. Special kinetic studies should explore the effects on pharmacokinetics of altered hepatic function. A difficulty, however, is that there is no convenient, widely applicable measure of liver function that can serve, as creatinine clearance does, as a predictor of how the excretion of many compounds will be altered. It may prove possible, however, as marker compounds like debrisoquin or aminopyrine are studied further, to define liver function in functionally relevant ways and link the kinetics of drugs to metabolism of the marker compounds. I think we are at the verge of major increases in our ability to assess the impact of altered hepatic function. Indeed, some at this workshop may well believe this is already possible if only people would pay attention to them.

   c. Carry out kinetic studies in the elderly.

There is some doubt in my mind about the usefulness of pharmacokinetic studies in the healthy elderly. So long as we remain aware that this will not necessarily predict outcomes in patients, they certainly cannot hurt and there is a fair consensus that they should be done.

What I continue to believe makes more sense is something quite different, and is based on the idea that what we need to know about is all of the factors that alter the usual or normal pharmacokinetics of the drug, even factors we do not suspect. We are most likely to discover such unexpected influences by studying many patients, with a variety of background conditions. Instead of a kinetic study in the elderly I had proposed a "pharmacokinetic screen," basically a one-or-two time sample of steady state blood concentrations of drug obtained from large numbers of patients, even all patients, in phase 3 trials. If the basic pharmacokinetics of the drug are known, it should be possible, after adjusting for the known factors that influence blood concentrations, such as dose, lean body weight and renal function, to determine whether the phase 3 patients have the expected or different blood concentrations. Unexpected values, i.e., values for individuals or whole patient sub-groups not predicted by the pharmacokinetic model would indicate that some other influence was active (age, disease, another drug) and these factors would be examined further. In some cases the pattern would be obviously linked to an underlying condition, such as CHF. In others it might be sporadic, perhaps resulting from metabolic heterogeneity. What is attractive to me in this is that it should be possible to look at many separate possible influences and their combinations, including influences not plausible enough to merit formal study, all at once. To do this in a series of trials would be difficult or impossible, and if possible extremely costly. It may be that, like alterations in renal function, age *per se* has so important an influence on pharmacokinetics that the elderly should routinely be studied, but that, I think, is yet to be shown and is unlikely. It still seems preferable to me to cast the widest net possible, by use of a screening approach, and follow up on the leads that emerge. If, after all, older people have significantly altered kinetics and are well-represented in the study population, one can hardly fail to detect altered blood concentrations of drug. Is it really likely that a kinetic study in 8-10 healthy people will give a more accurate picture than steady state concentrations in 300 patients? I am also reassured by the comments of Sheiner and others that it is realistic to expect, on the basis of as few as two measurements per patient of drug concentration at steady state, a meaningful assessment of significant alterations in pharmacokinetics in population subsets.

Despite my continued belief in the ultimate usefulness of the pharmacokinetic screen, I accept the idea that the proposal is too unfamiliar and untried to be required in a guideline. My plan therefore is that the guideline will offer two options - the screen or pharmacokinetic studies in the elderly. I am nonetheless very optimistic that the current effort by an ASCPT committee to evaluate available phase 3 blood level data will show the usefulness and practicality of the screening approach. We have recently made use of such blood level data in evaluating the assertion that the NSAID piroxicam accumulates in the elderly. While some pharmacokinetic data do indeed suggest this, blood level data from about 600 patients in a clinical trial showed only a small age-related increase in blood concentration. The screen lives.

d. Drug-drug and drug disease interactions.

If the drug is going to be used in conditions where specific concomitant diseases are particularly likely to be present, or other drugs are likely to be used, an attempt should be made to include patients with the other diseases or on the other drugs in the treatment population. The pharmacokinetic screen should be useful in determining whether the other diseases or drugs affect blood levels of the new drug, and clinical observations should permit detection of specific adverse effects associated with the other diseases. Where a drug is intended principally for a group with a condition likely to affect kinetics, e.g., patients with heart failure, a specific study in that patient group is needed.

It is also possible that the new drug will have an effect on the kinetics of other drugs, an important matter to the elderly who are more likely to be receiving other drugs. There is almost no limit to the number of studies that could be mounted to explore this question; therefore a second screening mechanism would be helpful. If Phase 3 clinical trials include patients who are on a variety of other drug therapies (held stable during introduction of the new agent), trough blood levels of the other drugs can be obtained prior to dosing with the new agent and again after the new agent has reached steady state. It should thus be possible to detect, with relatively little effort, major effects of the new drug on many concomitant medications. The principal limit to being able to do so will be the availability of good blood level measurements for the other agents. In general, drugs where blood levels are most critical are those for which blood level determinations are being developed.

While all of the preceding points have been discussed widely, I look forward to the formal guideline proposal. It will reflect the many helpful comments we have received and I probably will be discussing particular points with some of the people in this room before the proposal.

I do want to emphasize one point that may not be popular at a meeting devoted to geriatric clinical pharmacology. Most of the problems associated with drug use in older patients probably have little to do with age itself, i.e., geriatric pharmacology, and much to do with diseases and conditions that are more common or more severe in the elderly, but can be present at all ages. Our goal should be to discover all of the factors that influence the pharmacokinetics and pharmacodynamics of drugs and increase appreciation of them, so that we can design effective, safe drug regimens based on an adequate assessment of any patient. If interest in drug use in the elderly feeds interest in an improved understanding of all the factors, such as altered renal and hepatic function, concomitant illness and drug use, or changes in body muscle and and fat distribution, that can alter pharmacokinetics, and leads to better training in the assessment of these factors and improved ability to make rational dosing adjustment based on that assessment, patient care will be generally enhanced. The elderly, as major drug users, and as major possessors of these factors that complicate therapy, will benefit disproportionately. It would be disappointing, however, if we were to narrow our focus to the effects of age alone, and miss the rest.

The guideline proposal, which I expect to appear in early 1987, will reflect both the views expressed above and some of the alternative suggestions that have emerged in response to the discussion paper. I continue to believe that the attempt to anticipate and study formally pharmacokinetics and pharmacodynamics in all of the potentially important patient subsets of the elderly will usually be futile because the most important problems will arise in the more complicated patients who will not get into pharmacokinetic and other clinical pharmacology studies in adequate.numbers. We therefore must learn to use the entire investigational population as a source of clues to pharmacokinetic and pharmacodynamic differences. Even if I am wrong in being skeptical of the usefulness of formal clinical pharmacologic studies in the elderly, these screening approaches will be needed additions.

# # # # #

Item 14

National Adverse Drug Reaction Surveillance: 1985

Gerald A. Faich, MD, MPH; Deanne Knapp, PhD; Michael Dreis, RPh, MPH; Wayne Turner, PhD

The Food and Drug Administration received about 37 000 adverse drug reaction reports in 1985. Seventy-one percent of the reports involved toxic reactions to usual doses of drugs and were sent by medical care professionals directly to the Food and Drug Administration or to pharmaceutical manufacturers. In terms of severity, 2% of reports involved death while 21% involved hospitalization. The highest proportions of hospitalization or death were found for reports describing cardiovascular, hematologic, or respiratory effects. Nearly half of the reported deaths were in patients more than 59 years of age. The majority of reports described an adverse drug reaction occurring within two weeks of initial exposure to the suspected drug. Adverse drug reaction reporting by physicians is crucial to ensuring that pharmaceutical products are used appropriately.

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THE FOOD and Drug Administration (FDA) has long conducted a program to monitor reported adverse drug reactions (ADRs) for approved pharmaceutical products. Since 1969, data from this program have been computerized and over 300 000 reports have been received. In the past year, a number of changes have been made in the ADR program to increase its effectiveness and efficiency.[1] These include the issuance of new regulations for pharmaceutical manufacturers,[2,3] the initiation of pilot projects to stimulate physician reporting, and the use of new data processing and retrieval systems. This article presents a descriptive overview of the ADR reports received by the FDA during 1985.

The purpose of ADR surveillance is to detect potential safety problems of marketed drugs. Because of inherent limitations in preapproval testing, such as the size and duration restrictions of human clinical trials, this postmarketing activity is crucial to providing needed information about drugs. Historically, the need to collect ADRs centrally after marketing was recognized after the discovery of chloramphenicol-induced aplastic anemia[4] and thalidomide teratogenesis.[5] In addition to providing early warning signals about major unsuspected hazards, ADR surveillance contributes to the routine evolution of recommendations for use, precautions, and warning information provided with marketed pharmaceuticals.

In recent years there has been renewed interest in ADR surveillance. This has involved increased recognition of its value by the FDA and the pharmaceutical industry. In fact several major products have been withdrawn from the market based on postmarketing experience (eg, ticrynafen,[6] zomepirac sodium,[7] and benoxaprofen[8]); in 1986 a newly approved antidepressant, nomifensine, was withdrawn by the manufacturer because a relatively large volume of spontaneous reports of severe hemolytic anemia had accumulated.[9] There have also been major increases in the quantity of ADR reports received by the FDA. In the late 1970s and early 1980s, about 10 000 ADR reports per year were received by the FDA. This figure has risen dramatically in recent years—exceeding 30 000 in 1984 and approaching 40 000 in 1985.

Methods

The FDA receives ADR reports from pharmaceutical manufacturers and directly from the medical community. Manufacturers are required by regulation to submit to the FDA all reports they receive.[2,3] Most of these originate from practicing care providers who contact the pharmaceutical manufacturer when a suspected reaction is seen. Reports submitted by the industry are of two types: those involving serious and unlabeled reactions that must be promptly submitted by the manufacturer (15-day reports) and all others that must be submitted in a more routine manner (periodic reports). *Serious* in this context is defined as an outcome of death, hospitalization, prolongation of hospitalization, permanent disability, or receiving prescription drugs to treat the reaction. Reports of cancer and congenital defects are also considered serious. Direct reports to the FDA are sent by physicians or hospital-based pharmacists using a report form (FDA 1639) that is mailed periodically to care providers in the FDA's *Drug Bulletin*.

On receipt by the FDA, all direct reports and 15-day manufacturer reports are individually assessed. This assessment includes a determination about the need to obtain follow-up information and a search for similar reports already in the system. After consultation within the FDA, decisions are made about conducting confirmation studies and taking regulatory action.[10]

Results

In 1985 the FDA received and computerized 36 931 ADR reports. Of these, 19% were manufacturer reports derived from foreign sources, studies, or the medical literature (Table 1). Eight percent of reports involved overdoses or lack of efficacy, and 1% of reports were sent by nonprofessionals. The remaining 26 381 (71%) ADR reports described reactions reported by US medical care professionals directly to the FDA or through pharmaceutical manufacturers; these provide the basis for the subsequent analyses in this article.

About 10% of the 26 381 ADR reports were submitted directly to the FDA while 25% were manufacturer 15-day reports and 65% were manufacturer periodic reports (Table 2). In terms of severity, 2% of all reports involved death (with or without hospitalization) and 21% mentioned hospitalization or prolongation of hospitalization without death; the remainder did not mention death or hospitalization. As expected, manufacturer 15-day reports had a higher proportion of deaths and hospitalization than did manufacturer periodic reports. Importantly, the proportion of direct reports (33%) with death or hospitalization was the same as that found for manufacturer 15-day reports.

Using the primary sign, symptom, or

Table 1.—Adverse Drug Reaction (ADR) Reports Received by the Food and Drug Administration by Source, 1985

Source	No.	%
Foreign	4763	13
Study reports	2078	6
Literature and project	179	1
Nonprofessional reports	452	1
Overdose/lack of efficacy	3078	8
Domestic, professional ADR reports	26 381	71
Total	36 931	100

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The opinions expressed are those of the authors and do not necessarily represent those of the Food and Drug Administration.

Reprints not available.

Table 2.—Distribution of Adverse Drug Reaction Reports* by Source and Severity, 1985

	Severity		
Source	No.	% Died	% Hospitalized
Direct to the Food and Drug Administration reports	2671	2	31
Manufacturer 15-d reports	6533	5	28
Manufacturer periodic reports	17 177	1	17
Total	26 381	2	21

*Domestic spontaneous professional origin only.

Table 3.—Distribution of Adverse Drug Reaction Reports by Body System

Body System	No.	%
Body as a whole	5311	20
Cardiovascular	2648	10
Digestive	3048	12
Endocrine	163	1
Hemic and lymphatic	1503	6
Metabolic and nutritional	1153	4
Musculoskeletal	465	2
Nervous	4109	16
Respiratory	1080	4
Skin and appendages	3856	14
Special senses	1251	5
Urogenital	1985	8
Total	26 381	102*

*Percentages do not add up to 100 due to rounding.

Table 4.—Distribution of the US Population and 16 625 Adverse Drug Reaction Reports by Age and Severity, 1985

			Outcome (%)*	
Age, y	% of Population	% of Reports	Died	Hospitalized
≤19	30	17	2	24
20-39	34	28	1	23
40-59	20	25	2	28
≥60	17	30	4	33
Total	100	100	3	28

*Restricted to outcomes of reports with age given; thus, differs from Table 2.

Table 5.—Number of Adverse Drug Reaction Reports by Source and Drug Type*

	Reports			
Drug Type	Direct	15-d	Periodic	Total
NCEs	422	1358	3122	4902
Non-NCEs	2249	5175	14 055	21 479
Total	2671	6533	17 177	26 381

*NCE indicates new chemical entity approved and marketed between 1982 and 1985.

diagnosis given on a report form, ADR reports can be classified by the main body system affected. Twenty percent of the reports involved the body as a whole (shock, fever, anaphylaxis, etc) while 52% of the reports affected the cardiovascular, digestive, nervous, or dermatologic systems (Table 3). The highest proportions of hospitalization or death were found for reports describing cardiovascular (40%), hematologic (38%), or respiratory (37%) effects. Reports of hospitalization and death were almost evenly divided between men and women.

Age data were available for about two thirds of the ADR reports. For these, 17% and 30% were for patients younger than 20 years and older than 59 years of age, respectively (Table 4). The over-59-year-old age group accounted for 37% of reports involving hospitalization and 49% of reports involving death. Persons aged 60 years or older represent about 17% of the US population[illegible]; however, it is estimated that 39% of pharmaceutical exposure occurs in this age group.[illegible] Dates for initiation of therapy with the suspected drug and for onset of the reaction were given on only 35% of the ADR reports. From these reports it was found that 63% of the ADRs occurred within two weeks of exposure to the suspected drug.

Marketed drugs can be divided into two general categories, recently marketed new chemical entities (NCEs) and all other drugs (reformulations, older drugs, etc). From 1982 to 1985, there were 70 NCEs that remained on the market in 1985. Thirty-five of these NCEs represented drugs that would be routinely dispensed to outpatients. These outpatient NCEs had an estimated 60 million prescriptions dispensed in 1985.[illegible] For all other prescription drugs, there were 1488 million prescriptions in 1985.[illegible] Since there were 4902 reports for recent NCEs and 21 479 for other drugs (Table 5), it is clear that the NCE reporting rate greatly exceeds that for other drugs. Outpatient NCE reports were about two thirds of all 15-day or direct NCE reports. The NCE reports did not differ in the proportion mentioning death and hospitalization from other drugs except for the subset of NCEs whose use tends to be concentrated in hospitals. For these latter NCEs, 34% of reports mentioned death or hospitalization as opposed to 23% overall and 20% for NCEs not preponderantly used in the hospital.

Comment

The number of ADR reports reaching the FDA is increasing. These reports are important if the medical community is to benefit from observations made by individual practitioners about possible reactions to drugs. The data presented indicate that most such physician observations reach the FDA through the pharmaceutical manufacturers. The 36 931 ADR reports received in 1985 represented a 14% increase over 1984.

Since most reports come from manufacturers and since regulations governing manufacturer submission of reports were changed in August 1985, it will be important to monitor future trends in manufacturer submissions. Of the reports submitted by pharmaceutical manufacturers, it is clear that the serious, unlabeled reactions given in 15-day reports are most important.

About one third of the direct-to-FDA reports made by care providers involve hospitalization or death and thus these reports are also likely to be useful for identifying important and serious ADRs. Overall, the severity of the reports submitted to the FDA is impressive in that 23% involved hospitalization or death. Nineteen percent of all ADR reports were for recently marketed NCEs; this is desirable since most new and important safety findings discovered after marketing are made for these drugs.[illegible]

Adverse drug reaction surveillance should be viewed as a method to identify possible drug toxicity problems.[1] Associations reported must be viewed as preliminary because causality on a case-by-case basis is often uncertain and because underreporting and biased reporting make estimates of incidence nearly impossible. Signals derived from surveillance often require further study for confirmation and quantitation.

Physicians are urged to be alert to detecting ADRs, particularly for new drugs. When suspected, ADRs should be reported to the FDA or the manufacturer. These reports are crucial to ensuring that drug risks are rapidly identified and made known to physicians and patients. Preapproval testing alone will never be enough to ensure drug safety. Reporting by alert and conscientious practitioners is our best means to detect new, important drug safety leads[15] and should be seen as a moral duty of physicians.[16]

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Chlamydia trachomatis Infections in the United States

What Are They Costing Us?

A. Eugene Washington, MD; Robert E. Johnson, MD, MPH; Lawrence L. Sanders, Jr, MD

Chlamydia trachomatis has emerged as the most common sexually transmitted bacterial pathogen in the United States and is now recognized to cause substantial morbidity. To determine the economic consequences of chlamydial infections in the United States, we analyzed data from local, state, and national sources. We estimate that *C trachomatis* infections cost Americans over $1.4 billion per year in direct and indirect costs. Chlamydial infections in women account for 79% of this cost, although men and infants are also affected. Three fourths of the total cost is due to sequelae of untreated, uncomplicated infections. If the current rate of chlamydial infection persists, the projected annual costs will exceed $2.18 billion by 1990. Reducing the incidence of personal suffering and heavy economic burden imposed by *C trachomatis* infections requires establishment and maintenance of effective prevention/control programs.

(*JAMA* 1987;257:2070-2072)

INFECTIONS caused by *Chlamydia trachomatis* constitute the most common sexually transmitted disease in the United States. Over 4 million infections occur each year.[1] The clinical spectrum of chlamydial disease encompasses a formidable group of infections and complications affecting men, women, and infants.[2,3] While the substantial morbidity caused by *C trachomatis* infections is now recognized, little attention has been paid to what they cost.

In this article, we present an estimate of the annual direct and indirect economic costs of chlamydial infections in the United States based on analysis of national, state, and local data. Direct cost in our analysis refers to health care expenditures and represents the value of goods and services actually used to treat *C trachomatis* infection and its effects; charges for medical care are used to approximate these costs. Indirect cost refers to lost productivity and represents the value of output forgone by patients suffering from *C trachomatis* infection and its sequelae.

Frequency of *C trachomatis* Diagnoses and Health Care Visits

Men.—Costs of chlamydial infections in men can be attributed to episodes of urethritis and of epididymitis. To estimate the annual frequency of diagnosis of chlamydial urethritis, we obtained data from the Centers for Disease Control's (CDC's) National Reporting System for gonorrhea and published reports. We also surveyed clinics in eight areas of the United States, selected both because of their geographic dispersion and because they performed laboratory tests to diagnose both *C trachomatis* and *Neisseria gonorrhoeae* infections. Data from these eight sentinel sites for 1983 through 1985 and published reports of studies covering 1980 through 1982 were used to establish a case ratio of *C trachomatis* to *N gonorrhoeae* infection. Overall, an average of 1.4 chlamydia diagnoses were made for each gonorrhea diagnosis. For this same period (1980 through 1985), the CDC estimates that an average of 1 107 200 cases of gonorrhea were diagnosed annually among men. Multiplying this national incidence of gonorrhea cases by our case ratio of chlamydia to gonorrhea diagnoses, we estimate that 1.55 million diagnosed episodes of clinical illness due to *C trachomatis* occur annually in men. Additional details about these estimates have been published elsewhere.[1]

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Reprint requests to Technical Information Services, Center for Prevention Services, Centers for Disease Control, Atlanta, GA 30333.

Chlamydia trachomatis Infections—Washington et al

Item 15

THE ADVERSE DRUG REACTION ANNUAL REPORT: 1985

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INTRODUCTION

The U.S. Food and Drug Administration (FDA) has long conducted a program to monitor reported adverse drug reactions (ADRs) for approved drugs. Since 1969, data from this program have been computerized, and over 280,000 reports have accumulated in the database. In the past year, a number of changes have been made in the ADR program to increase its effectiveness and efficiency.[1] This paper presents a descriptive overview of the ADR reports received by FDA during 1985.

ADR REPORTS RECEIVED DURING 1985

General Information

There were 36,931 ADR reports received and computerized by FDA during 1985 of which 4,763 (13%) came from foreign sources. Of the remaining 32,168 (87%) domestic ADR reports, 6% were from manufacturers for drugs being investigated in formal studies, 1% were from the published literature or special projects, and 93% (29,911 reports) were primarily from health professionals and described suspected ADRs based on observations made during their usual provision of care to patients. A health professional ADR report reaches FDA by one of two routes: (a) the health professional sends the report directly to FDA, or (b) the health professional reports the ADR to the drug manufacturer who is required by law and regulation to send such a report to FDA.[2] Of the 29,911 reports based on observations primarily by health professionals, 10% mentioned overdose or lack of efficacy as the adverse drug experience, leaving 26,833 (90%) reports in which an ADR was associated with a drug administered within its therapeutic dosage range and without a problem with the drug's therapeutic effect.

Profile of ADR Reports

Types of Reports and Outcomes. Continuing with the ADR reports of drugs administered within an effective/therapeutic dosage range, we focused on three types of reports and three outcomes associated with reactions in the reports. The types of reports were: (a) reports from manufacturers which contained an ADR not presently in the official labeling and a serious outcome (ie, death, hospitalization or prolongation of hospitalization, permanent disability, or treatment with a prescription drug was required); (b) all other reports from manufacturers; and (c) reports submitted directly to FDA by health professionals. Omitted from further analyses were 452 reports consisting primarily of reports from persons who were not health professionals.

The selected outcomes were: (a) death, (b) hospitalization or prolongation of hospitalization without death, and (c) all other outcomes, including no reported outcome. This 3 x 3 schema was utilized to profile the ADR reports in several ways.

Table 1 (see next page) shows the disaggregation of the ADR reports utilizing the 3 x 3 design as well as a portrayal of the body systems associated with the ADRs in the reports. During routine computer processing of the reports, each ADR term is standardized and assigned to one or more body systems.[3] Since the median number of ADRs per report was one, in order to eliminate doublecounting in the analyses, only the first-listed ADR in each report was used. For the same rationale, only one body system per ADR term and the first-reported suspect drug were utilized.

As can be seen from Table 1, there was a total of 26,381 reports of which 90% were from manufacturers. All the manufacturers were ranked by their number of reports for 1985. The top 20 manufacturers accounted for 75% of all manufacturer reports.

Of the 23,710 manufacturer reports, about one-quarter were for nonlabeled ADRs with serious outcomes. Hospitalization (or its prolongation) and death accounted for: (a) about one-third of the manufacturer reports of nonlabeled ADRs and direct health professional reports and (b) about one-fifth of all other manufacturer reports.

Body Systems. For all manufacturer reports with hospitalization (see Table 1), the three top ranked body systems accounting for about half of these reports were: body as a whole, the cardiovascular system, and the nervous system. For direct health professional reports, the skin and appendages system, instead of the nervous system, with the cardiovascular system and body as a whole were the top three systems which accounted for about half of the hospitalization reports.

For all manufacturer reports with death as the outcome, one body system was associated with a little over half of these reports -- body as a whole. For direct health professional reports, about half of their death reports were linked with two body systems -- body as a whole and the cardiovascular system.

Demographics. Table 2 (see next page) presents the demographic information for the three types of reports and three outcomes. Age was reported for about 60% of all reports; sex,. 80% of all reports. Generally, these percentages were higher for reports noting hospitalization or death. Direct health professional reports were associated with the highest rates of completion for this information.

Although ≥ 60 year-olds represent about 17% of the U.S. population,[4] they were associated, not unexpectedly, with about one-third of the hospitalization reports and about one-half of the death reports. The reports of hospitalization and death were almost evenly divided between females and males, reflecting U.S. population.[4]

Drug Treatment and Adverse Reactions. Table 3 (see next page) shows the frequency distribution of ADR reports by the time interval between the suspect drug's initiation and ADR onset. Only about one-third of the ADR reports had this information. Again, direct health professional reports had a higher completion rate for this information -- about 60% of their reports had these data. Nearly all (90%) of the ADRs had their onset within six months of when the reported suspect drug was started.

Table 1. Frequency of Types of Reports and Types of Outcomes and Their Distribution by Body System, 1985.

	All Types of Reports and Outcomes		Manufacturer Reports Containing Nonlabeled ADRs and Serious Outcomes			All Other Manufacturer Reports			Direct, Health Professional Reports		
	N	%	Hosp Only[a]	Death	Other Outcomes[b]	Hosp Only[a]	Death	Other Outcomes[b]	Hosp Only[a]	Death	Other Outcomes[b]
All Body Systems	26,381	100*	1,851	321	4,361	2,858	257	14,062	823	43	1,805
Body As A Whole	5,311	20	318	176	1,236	465	162	2,479	134	10	331
Cardiovascular	2,648	10	335	47	399	521	21	1,045	122	11	147
Digestive	3,048	12	207	16	399	350	17	1,777	85	5	192
Endocrine	163	1	19	0	29	18	2	85	2	0	8
Hemic & Lymphatic	1,503	6	156	26	244	253	18	561	106	9	130
Metabolic & Nutritional	1,153	4	75	3	161	140	5	709	11	2	47
Musculoskeletal	465	2	27	0	117	41	1	247	6	0	26
Nervous	4,109	16	325	25	732	453	14	2,170	113	2	275
Respiratory	1,080	4	150	9	168	169	9	427	59	1	88
Skin & Appendages	3,655	14	92	5	407	216	3	2,378	135	2	417
Special Senses	1,251	5	37	0	204	59	0	854	18	0	79
Urogenital	1,995	8	110	14	265	173	5	1,330	32	1	65

a Outcome of hospitalization or prolongation of hospitalization without death.
b Includes no reported outcome.
* Percentages may not total to 100 due to rounding error.

Table 2. Frequency of Types of Reports and Types of Outcomes Distributed by Age and Sex, 1985.

	All Types of Reports and Outcomes		Manufacturer Reports Containing Nonlabeled ADRs and Serious Outcomes			All Other Manufacturer Reports			Direct, Health Professional Reports		
	N	%	Hosp Only[a]	Death	Other Outcomes[b]	Hosp Only[a]	Death	Other Outcomes[b]	Hosp Only[a]	Death	Other Outcomes[b]
All Known Age (In years)	16,625	100	1,576	224	2,742	2,259	174	7,347	747	39	1,517
≤19	2,795	17	278	49	741	274	13	1,071	111	7	251
20-39	4,702	28	341	36	730	581	21	2,332	182	3	476
40-59	4,084	25	396	36	606	572	47	1,885	171	9	362
≥ 60	5,044	30	561	103	665	832	93	2,059	283	20	428
All Known Sex	21,222	100	1,727	249	3,429	2,571	218	10,590	776	42	1,620
Female	12,399	58	888	126	1,963	1,419	109	6,484	435	21	954
Male	8,823	42	839	123	1,466	1,152	109	4,106	341	21	666

a,b See Table 1.

Table 3. Frequency of Types of Reports and Types of Outcomes Distributed By Interval Between Suspect Drug Initiation and Adverse Drug Reaction Onset, 1985.

	All Types of Reports and Outcomes		Manufacturer Reports Containing Nonlabeled ADRs and Serious Outcomes			All Other Manufacturer Reports			Direct, Health Professional Reports		
	N	%	Hosp Only[a]	Death	Other Outcomes[b]	Hosp Only[a]	Death	Other Outcomes[b]	Hosp Only[a]	Death	Other Outcomes[b]
All Known Intervals (In days)	9,345	100*	958	128	1,274	1,448	106	3,798	573	28	1,032
≤ 1	3,604	39	329	38	434	603	27	1,452	250	9	462
2- 14	2,210	24	258	42	246	367	30	829	162	4	272
15-182	2,589	28	279	35	401	345	31	1,149	127	10	212
≥ 183	942	10	92	13	193	133	18	368	34	5	86

a,b,* See Table 1.

A dechallenge of the suspected drug was listed for 10,926 (41%) of all ADR reports. Reports with hospitalization had the highest percentage of dechallenges noted (59%). Only 7% of all reports stated that a rechallenge was performed.

New Chemical Entities. Table 4 (see next page) presents the frequency distribution of the types of reports and outcomes by new chemical entity (NCE) information. There were 70 NCEs approved and first marketed during 1982-5 which are still marketed. Each of these NCEs was classified as to whether it was the type of drug that: (a) would be more likely to be routinely dispensed to patients by prescription through retail pharmacies or (b) would not be expected to be distributed in this manner, eg, drugs only administered intravenously.

About one-fifth of all ADR reports were for the NCEs. Retail pharmacy NCEs accounted for half of the NCEs; however, they provided three-quarters of the NCE reports. Hospitalization and death outcomes accounted for: (a) 20% of the retail pharmacy NCE reports, (b) 34% of the nonretail pharmacy NCE reports, and (c) 23% of the nonNCE reports.

SUMMARY

In reviewing FDA's ADR reports for 1985, manufacturers contributed nearly all (90%) of the domestic spontaneous ADR reports with about 10% of their reports noting hospitalization or death in association with a nonlabeled adverse reaction. Twenty drug manufacturers contributed 75% of all manufacturer reports. Thus, in effect, 20 manufacturers were associated with about two-thirds of the domestic spontaneous ADR reports in 1985. Reports on NCEs marketed during 1982-5 accounted for about 20% of all ADR reports during 1985.

Although the proportion of direct health professional reports was small, their reports were more complete on key items necessary for drug-adverse event interpretations. This finding is consistent with a recent evaluation of FDA's ADR reports which showed that direct health professional reports contributed significantly to the detection of new ADRs that eventually became part of the official labeling.[5]

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Table 4. Frequency of Types of Reports and Types of Outcomes Distributed by Type of Drug, 1985.

	All Types of Reports and Outcomes		Manufacturer Reports Containing Nonlabeled ADRs and Serious Outcomes			All Other Manufacturer Reports			Direct, Health Professional Reports		
	N	%	Hosp Only[a]	Death	Other Outcomes[b]	Hosp Only[a]	Death	Other Outcomes[b]	Hosp Only[a]	Death	Other Outcomes[b]
All Types of Drugs	26,381	100	1,851	321	4,361	2,858	257	14,062	823	43	1,805
NCEs*(n=70)	4,902	19	412	45	901	555	37	2,530	116	7	299
Pharmacy** (n=35)	3,690	-	273	32	580	349	20	2,144	77	4	211
Nonpharmacy(n=35)	1,212	-	139	13	321	206	17	386	39	3	88
NonNCEs	21,479	81	1,439	276	3,460	2,303	220	11,532	707	36	1,506

a,b See Table 1.

* New Chemical Entities approved and first marketed during 1982-5 which are still marketed.

** NCEs that would more likely be routinely dispensed to patients by prescription through retail pharmacies.

Item 16

Second Annual Adverse Drug/Biologic Reaction Report:1986

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INTRODUCTION

The US Food and Drug Administration (FDA) has long conducted a program to monitor adverse reactions (ARs) for approved drugs and licensed biologics. Since 1969, AR data have been computerized, and about 350,000 reports have accumulated in the database. This paper presents a descriptive overview of the AR cases received by FDA during 1986 and pertinent changes from 1985.

GENERAL INFORMATION

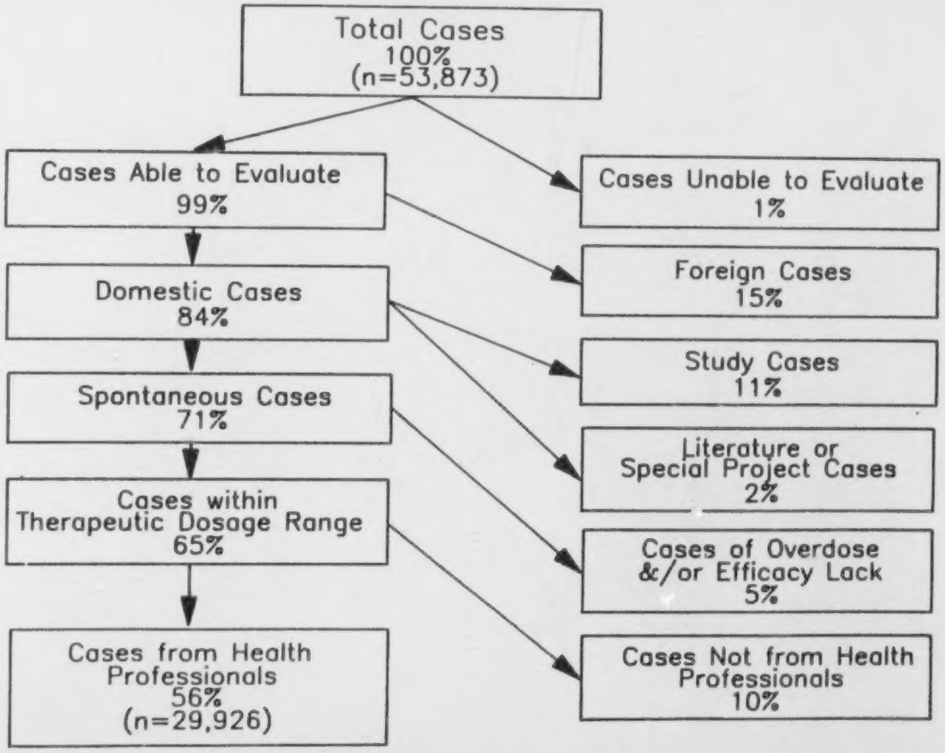
1986 Data

There were 53,873 AR cases received and computerized by FDA during 1986. Figure 1 presents the cascade of these cases. About half of the cases (n=29,926) were reported domestically by health professionals during routine care of patients who had been administered drugs or biologics within the therapeutic dosage range.

Changes from 1985 Data

The most noticeable change was the percent of cases from health professionals; in 1985, it was 71% while in 1986, it was 56%. This apparent drop in health professional reporting was probably artifactual, created by a change in the AR reporting form; in the 1986 version, there was better ascertainment of the source of the report.

Figure 1: Cascade of Adverse Reaction (AR) Cases Received and Computerized by FDA During 1986


Total Cases
100%
(n=53,873)
Cases Able to Evaluate
99%
Cases Unable to Evaluate
1%
Domestic Cases
84%
Foreign Cases
15%
Spontaneous Cases
71%
Study Cases
11%
Literature or
Special Project Cases
2%
Cases within
Therapeutic Dosage Range
65%
Cases of Overdose
&/or Efficacy Lack
5%
Cases from Health
Professionals
56%
(n=29,926)
Cases Not from Health
Professionals
10%

PROFILE OF ADVERSE REACTION CASES

Explanatory Remarks and Glossary

All subsequent analyses and tables, unless noted otherwise, are based on the 29,926 evaluable domestic, spontaneous cases received either directly from health professionals or indirectly from health professionals via pharmaceutical manufacturers and computerized by FDA in 1986. These cases contain information on adverse events to marketed drugs or biologics which had been administered within therapeutic dosage ranges. The percentages in the subsequent tables and figures may not total to 100% due to rounding errors. Unless specifically noted otherwise, it is to be assumed that for each analysis, the respective 1985 distribution of cases was similar.

The following is a glossary of the terms as used in this report:

All Other Manufacturer Case=	case sent by a health professional to a pharmaceutical manufacturer where the first-listed suspect drug/biologic reported was associated with a nonserious adverse reaction or with a serious adverse reaction presently in the official labeling; by law and regulation, the manufacturer is required to send such drug case reports (but not biologic reports) to FDA; also known as a "periodic" case.
AR =	adverse reaction suspected by the health professional of being drug or biologic associated; only the first-listed AR of a case is included in the analyses (to prevent multiple counting).
Body System =	body system associated with the reported AR; only the primary body system per AR is included in the body system analyses (to prevent multiple counting). Refer to Appendix 1 for descriptions of the body systems.
Case =	original report of AR on a patient plus any follow-up information; this collation of information prevents multiple counting.
Death =	reported outcome of death; may or may not include prior hospitalization.
Direct, Health Professional Case =	case sent by a health professional directly to FDA; also known as a "direct" case.
Drug/Biologic =	marketed drug/biologic reported by a health professional as being associated with an AR; only the first-listed suspect drug or biologic for a case is included in the analyses (to prevent multiple counting).
Hospitalization = (Hosp)	reported outcome of hospitalization or prolongation of hospitalization without death; excludes cases where death was the reported outcome.
Interval =	number of days between initiation of treatment with the first-listed suspect drug or biologic and occurrence of the first-listed AR.
Manufacturer Case Containing Nonlabeled AR(s) and Serious Outcome(s) =	case sent by a health professional to a pharmaceutical manufacturer where the first-listed suspect drug/biologic reported was associated with an AR not presently in the official labeling and where a serious outcome occurred (ie, death, hospitalization, permanent disability, treatment with a prescription drug, congenital anomaly, or cancer); by law and regulation, the manufacturer is required to send such drug case reports (but not biologic reports) to FDA within 15 working days; also known as a "15-day" case.
Other Outcome = (Other)	outcome other than death or hospitalization, including no reported outcome.
Permanent Disability =	permanent and substantial disruption of one's ability to perform normal activities.

Recent New Chemical or Biological Entity (NCBE) = new chemical or biological entity first approved and marketed during 1983-86 and which is still being marketed.

Spontaneous Case = case based on observations made by a health professional during usual provision of patient care.

Therapeutic Class =therapeutic class of drugs/biologics associated with the AR; the classification scheme was adapted from the American Hospital Formulary Service (see Appendix 2); only one therapeutic class per first-listed suspect drug or biologic is included in the therapeutic class analyses to prevent multiple counting).
The following class abbreviations were used in this report:
CNS=central nervous system agents
CV=cardiovascular drugs
DX=diagonostic agents
HORM=hormones and synthetic substitutes
INF=anti-infective agents
NEO=antineoplastic agents
SKIN=skin and mucous membrane agents
STV=serums, toxoids, and vaccines

* (in a table) = <1%.

Types of Cases and Outcomes

In both 1985 and 1986, cases from manufacturers accounted for about 90% of evaluable, domestic, spontaneous cases reported by health professionals where the suspect drug/biologic was within the therapeutic dosage range (within-scope cases). Also in both years, about 75% of the manufacturer-reported cases were submitted by 20 manufacturers.

Three types of cases were defined by source of report as follows:

1. Manufacturer-reported cases containing nonlabeled ARs and serious outcomes (in regulatory language known as "15-day" reports).
2. All other manufacturer-reported cases (in regulatory language known as "periodic" reports).
3. Direct, health professional-reported cases received directly by FDA from health professionals ("direct" reports).

Three types of outcomes were defined:

1. Death
2. Hospitalization
3. All other outcomes

Figures 2 and 3 and Table 1 give an overall picture of the within-scope cases by type of case, type of outcome, and crossclassified by type of case and outcome, respectively. Figure 2 shows that nearly all cases (91%) were received from manufacturers, and 15% of all cases were manufacturer cases containing nonlabeled ARs with serious outcomes. Only 9% of cases were directly reported to the FDA by health professionals. In Figure 3, note that about one-fifth of the cases had a reported outcome of either death or hospitalization.

Table 1 disaggregates the data further and shows that two-thirds of the cases were "all other manufacturer" cases containing "other outcomes." Manufacturer cases containing nonlabeled ARs and the serious outcomes of death or hospitalization accounted for 8% of cases. Death or hospitalization was reported in 18% (4,951/27,127) of manufacturer cases versus 31% (877/2,799) of the direct, health professional cases.

Figure 2: Distribution of Cases by Type of Case
n=29,926 (100%)

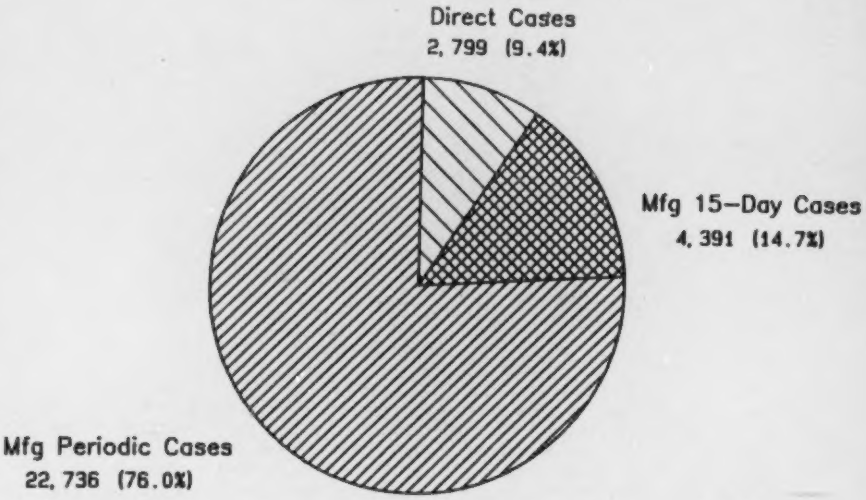


Figure 3: Distribution of Cases by Outcome
n=29,926 (100%)

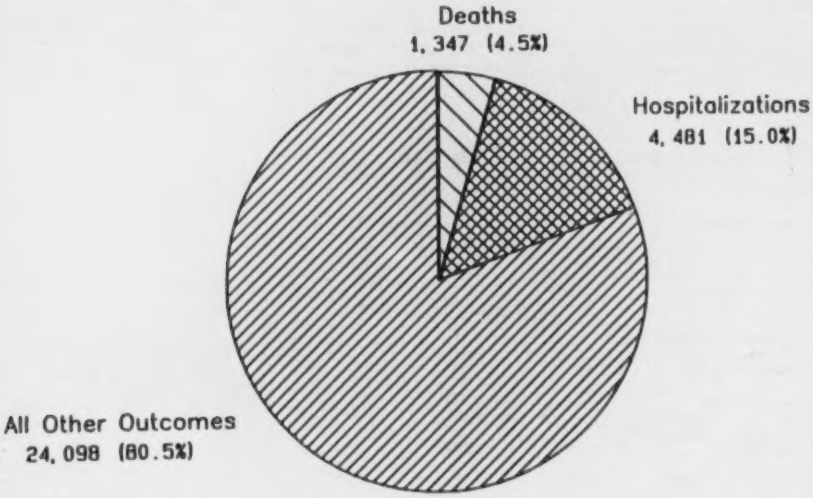


Table 1. Distribution of Cases by Type of Case and Outcome

	Type of Case					
	Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes		All Other Manufacturer Cases		Direct, Health Professional Cases	
Type of Outcome	N	%	N	%	N	%
Death	797	3	364	1	186	1
Hospitalization	1,591	5	2,199	7	691	2
Other Outcomes	2,003	7	20,173	67	1,922	6

Total Cases= 29,926 = 100%

Body Systems

Table 2 and Figure 4 show that cases reporting ARs that affected the "body as a whole" (see Appendix 1) ranked first in frequency. This body system, along with the "skin and appendages" system and the "nervous" system, accounted for about one-half of the cases. Tables 3-4 and Figures 5-6 display the body system data stratified by type of case, outcome, and Table 5 crossclassifies the data by case and outcome.

In Table 3 note that the most frequently received type of case was an "all other manufacturer" "body as a whole" case. For each of the types of manufacturer cases, "body as a whole" cases accounted for 20% of the cases; for the direct cases, "skin and appendages" cases were associated with 21% of the cases.

Of interest in Table 4 is that two classes of cases, "body as a whole" with "other outcome" and "skin and appendages" with "other outcome" represented nearly one-third of all cases received. The crossclassified data (Table 5) show that "all other manufacturer" cases reporting "other outcomes" for the two aforementioned systems accounted for about one-quarter of all cases.

Table 2. Distribution of Cases by Body System

Body System	N	%
Body As A Whole	5,879	20
Cardiovascular	2,650	9
Digestive	3,533	12
Endocrine	144	*
Hemic & Lymphatic	1,766	6
Metabolic & Nutritional	1,540	5
Musculoskeletal	558	2
Nervous	4,356	15
Respiratory	1,361	5
Skin & Appendages	5,000	17
Special Senses	1,307	4
Urogenital	1,832	6

Total Cases= 29,926 = 100%

Figure 4: Distribution of Cases by Body System

n=29,926 (100%)

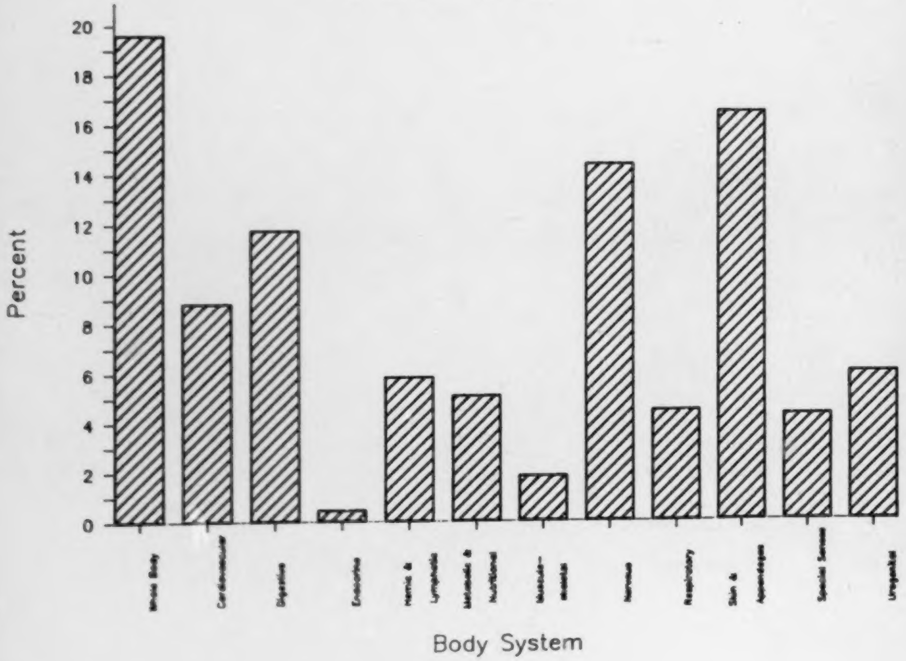


Table 3. Distribution of Cases by Body System and Type of Case

	Type of Case					
	Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes		All Other Manufacturer Cases		Direct, Health Professional Cases	
Body Sytem	N	%	N	%	N	%
Body As A Whole	881	3	4,450	15	548	2
Cardiovascular	606	2	1,753	6	291	1
Digestive	406	1	2,876	10	251	1
Endocrine	32	*	100	*	12	*
Hemic & Lymphatic	330	1	1,200	4	236	1
Metabolic & Nutritional	182	1	1,289	4	69	*
Musculoskeletal	89	*	444	1	25	*
Nervous	704	2	3,234	11	418	1
Respiratory	287	1	896	3	178	1
Skin & Appendages	357	1	4,042	14	601	2
Special Senses	189	1	1,038	3	80	*
Urogenital	328	1	1,414	5	90	*

Total Cases= 29,926 = 100%

Figure 5: Distribution of Cases by Body System and Type of Case

n=29,926 (100%)

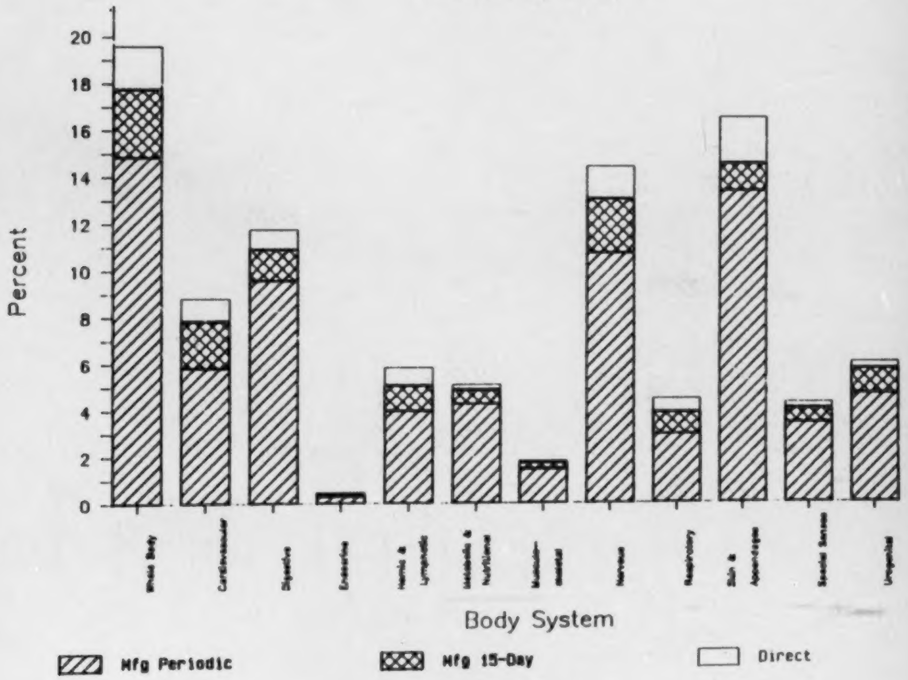


Table 4. Distribution of Cases by Body System and Type of Outcome

Type of Outcome

	Death		Hospitalization		Other Outcomes	
Body System	N	%	N	%	N	%
Body As A Whole	304	1	747	2	4,828	16
Cardiovascular	330	1	566	2	1,754	6
Digestive	128	*	617	2	2,788	9
Endocrine	3	*	29	*	112	*
Hemic & Lymphatic	153	1	466	2	1,147	4
Metabolic & Nutritional	34	*	241	1	1,265	4
Musculoskeletal	6	*	63	*	489	2
Nervous	125	*	667	2	3,564	12
Respiratory	123	*	289	1	949	3
Skin & Appendages	44	*	353	1	4,603	15
Special Senses	9	*	87	*	1,211	4
Urogenital	88	*	356	1	1,388	5

Total Cases= 29,926 = 100%

Figure 6: Distribution of Cases by Body System and Outcome
n=29,926 (100%)

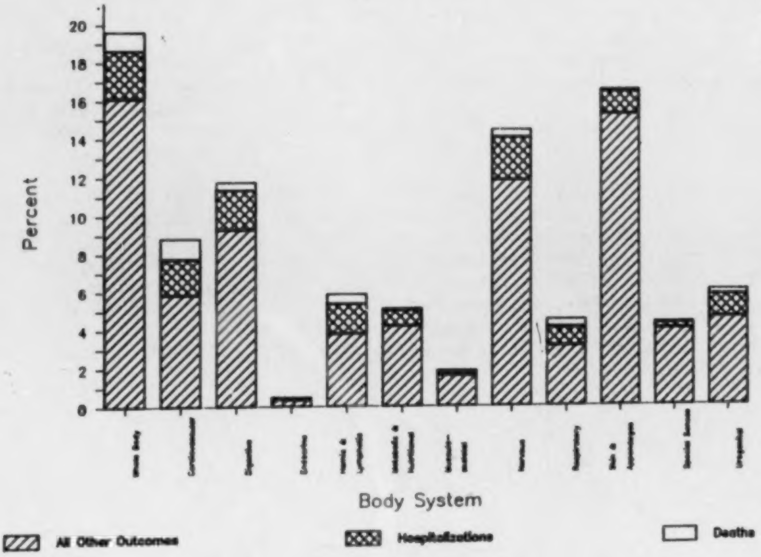


Table 5. Distribution of Cases by Body System and Type of Case and Outcome

Body System	Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes Death N	%	Hosp N	%	Other N	%	All Other Manufacturer Cases Death N	%	Hosp N	%	Other N	%	Direct, Health Professional Cases Death N	%	Hosp N	%	Other N	%
Body As a Whole	188	1	216	1	477	2	81	*	419	1	3,950	13	35	*	112	*	401	1
Cardiovascular	185	1	232	1	189	1	95	*	247	1	1,407	5	46	*	87	*	158	1
Digestive	74	*	205	1	127	*	40	*	333	1	2,503	8	14	*	79	*	158	1
Endocrine	1	*	14	*	17	*	1	*	11	*	88	*	1	*	4	*	7	*
Hemic & Lymphatic	78	*	147	*	113	*	44	*	228	1	920	3	39	*	91	*	106	*
Metabolic & Nutritional	24	*	85	*	73	*	7	*	139	*	1,143	4	3	*	17	*	49	*
Musculoskeletal	4	*	33	*	52	*	1	*	23	*	428	1	1	*	7	*	17	*
Nervous	87	*	279	1	338	1	28	*	280	1	2,926	10	10	*	108	*	300	1
Respiratory	72	*	113	*	102	*	32	*	133	*	731	2	19	*	43	*	116	*
Skin & Appendages	26	*	68	*	263	1	10	*	173	1	3,859	13	8	*	112	*	401	2
Special Senses	5	*	47	*	137	*	3	*	35	*	1,000	3	1	*	5	*	74	*
Urogenital	61	*	152	1	115	*	10	*	178	1	1,218	4	9	*	26	*	55	*

Total Cases= 29,926 =100%

Dechallenge and Rechallenge Information

On the AR reporting form, a health professional can indicate: (1) if the suspect drug/biologic was stopped and, if so, whether or not the reaction abated (ie, positive or negative dechallenge, respectively); (2) if, after the suspect drug/biologic was stopped and the AR abated, whether or not the reaction reappeared when the drug/biologic was reintroduced (ie, positive or negative rechallenge, respectively). Figures 7-8 present dechallenge/rechallenge information, while Tables 6-8 present these data stratified by type of case, outcome, and crossclassified by case and outcome.

Figures 7-8 show that although about 40% of the cases contained information regarding dechallenge, with about one-third of the cases indicating a positive dechallenge, positive rechallenge cases were few. Table 6 indicates that the majority of positive dechallenge/rechallenge cases were "all other manufacturer" cases. Table 7 shows, not surprisingly, that most positive dechallenge/rechallenge cases occurred with outcomes other than death or hospitalization. Table 8 notes that the greatest number of dechallenge/rechallenge positive cases occurred for "all other manufacturer" cases with "other outcomes."

Figure 7: Distribution of Cases by Dechallenge Information
n=29,926 (100%).

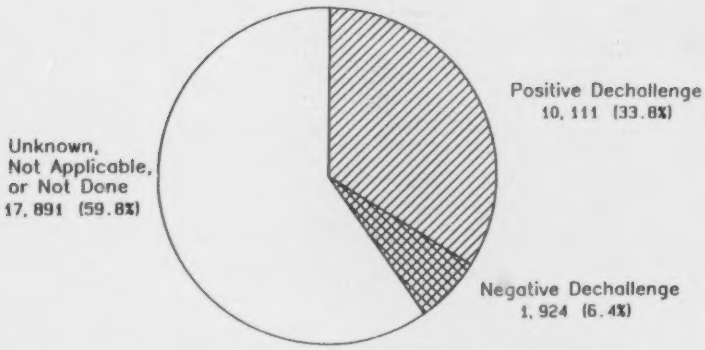


Figure 8: Distribution of Cases by Rechallenge Information
n=29,926 (100%)

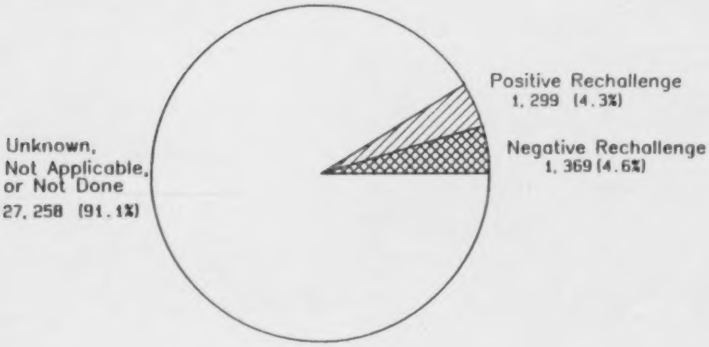


Table 6. Distribution of Cases by Dechallenge/Rechallenge Information and Type of Case

	Type of Case					
	Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes		All Other Manufacturer Cases		Direct, Health Professional Cases	
Type of Information	N	%	N	%	N	%
Dechallenge Info						
Unk/NA	2,717	9	13,744	46	1,430	5
+ dechallenge	1,153	4	7,767	26	1,191	4
- dechallenge	521	2	1,225	4	178	1
Rechallenge Info						
Unk/NA	4,140	14	20,777	69	2,341	8
+ rechallenge	162	1	972	3	165	1
- rechallenge	89	*	987	3	293	1

Total Cases= 29,926 = 100%

Table 7. Distribution of Cases by Dechallenge/Rechallenge Information and Type of Outcome

	Type of Outcome					
	Death		Hospitalization		Other Outcomes	
Type of Information	N	%	N	%	N	%
Dechallenge Info						
Unk/NA	1,032	3	2,157	7	14,702	49
+ dechallenge	71	*	1,866	6	8,174	27
- dechallenge	244	1	458	2	1,222	4
Rechallenge Info						
Unk/NA	1,298	4	4,065	14	21,895	73
+ rechallenge	17	*	192	1	1,090	4
- rechallenge	32	*	224	1	1,113	4

Total Cases= 29,926 = 100%

Table 8. Distribution of Cases by Dechallenge/Rechallenge Information and Type of Case and Outcome

	Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes						All Other Manufacturer Cases						Direct, Health Professional Cases					
	Death		Hosp		Other		Death		Hosp		Other		Death		Hosp		Other	
Type of Information	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Dechallenge Info																		
Unk/NA	631	2	845	3	1,241	4	268	1	1,022	3	12,454	42	133	*	290	1	1,007	3
+ dechallenge	32	*	543	2	578	2	26	*	975	3	6,766	23	13	*	348	1	830	3
- dechallenge	134	*	203	1	184	1	70	*	202	1	953	3	40	*	53	*	85	*
Rechallenge Info																		
Unk/NA	781	3	1,499	5	1,860	6	356	1	1,994	7	18,427	62	161	1	572	2	1,608	5
+ rechallenge	10	*	54	*	98	*	3	*	102	*	867	3	4	*	36	*	125	*
- rechallenge	6	*	38	*	45	*	5	*	103	*	879	3	21	*	83	*	189	1

Total Cases= 29,926 = 100%

Recent New Chemical and Biological Entities (NCBEs)

There were 69 NCBEs. In Figure 9, note that approximately 20% of the total cases (n=6,029) involved a suspect drug/biologic which was a NCBE.

In Table 9, 3% of the total cases involved ARs associated with NCBEs among the "manufacturer-reported nonlabeled ARs with serious outcomes" cases. For each of the types of manufacturer cases, NCBE cases accounted for one-fifth to about one-quarter of the cases; for the direct cases, NCBE cases were associated with 16% of the cases.

With respect to outcome, Table 10 shows that 4% of all cases were of deaths or hospitalizations associated with NCBEs. Crossclassification of the data in Table 11 shows that 2% of all cases were of reported deaths or hospitalizations which were "manufacturer-reported nonlabeled ARs with serious outcomes" cases associated with a NCBE.

Figure 9: Distribution of Cases by Drug/Biologic Type
n=29,926 (100%)

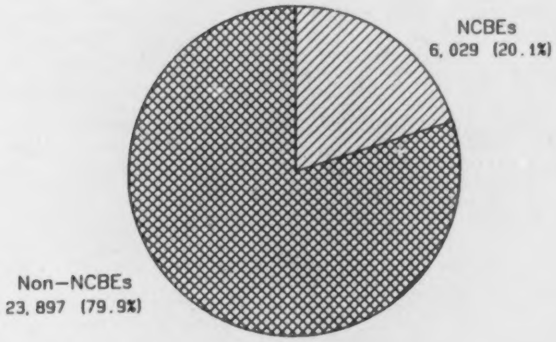


Table 9. Distribution of Cases by Type of Drug/Biologic and Type of Case

Type of Drug/Biologic	Type of Case Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes		All Other Manufacturer Cases		Direct, Health Professional Cases	
	N	%	N	%	N	%
NCBEs	1,025	3	4,558	15	446	1
NonNCBEs	3,366	11	18,178	61	2,353	8

Total Cases= 29,926 = 100%

Table 10. Distribution of Cases by Type of Drug/Biologic and Outcome

Type of Drug/Biologic	Type of Outcomes Death		Hospitalization		Other Outcomes	
	N	%	N	%	N	%
NCBEs	299	1	1,024	3	4,706	16
NonNCBEs	1,048	4	3,457	12	19,392	65

Total Cases= 29,926 = 100%

Table 11. Distribution of Cases by Type of Drug/Biologic, Case, and Outcome

Type of Drug	Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes						All Other Manufacturer Cases						Direct, Health Professional Cases					
	Death		Hosp		Other		Death		Hosp		Other		Death		Hosp		Other	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
NCBEs	175	1	430	1	420	1	87	*	466	2	4,005	13	37	*	128	*	281	1
NonNCBEs	622	2	1,161	4	1,583	5	277	1	1,733	6	16,168	54	149	*	563	2	1,641	5

Total Cases= 29,926 = 100%

Top Five Ranked Therapeutic Classes

This section is new with the 1986 review. Prior to about March 1986, the suspect drugs/biologics were not classified according to therapeutic action. The therapeutic clasification of the first suspect drug/biologic was available for 27,719 (93%) of the cases in 1986. Therefore, the denominator for this section of the analyses is 27,719 cases rather than 29,926 cases. Table 12 lists the Top Five ranked therapeutic classes for the 27,719 cases. Note that one-fifth of the cases involved a suspect drug/biologic with CNS activity.

Tables 13-15 show the Top Five therapeutic classes ranked by type of case, outcome and by crossclassification of case with outcome. In Table 13, note that CNS agents consistently ranked first regardless of type of case. For both types of manufacturer cases, CV drugs ranked second but for directly-reported cases, INF agents ranked second.

Looking at type of outcome, in Table 14, the same therapeutic classes were always ranked one through three regardless of outcome. Table 15 lists the rankings of therapeutic classes within each crossclassified stratum. Here, although CNS agents usually ranked first, among "all other manufacturer" cases and "direct, health professional" cases with death as the outcome, other therapeutic classes ranked first.

Table 12. Top Five Ranked Therapeutic Classes

Class	N	%
1. CNS	5,448	20
2. CV	4,322	16
3. INF	3,122	11
4. DX	2,192	8
5. HORM	1,770	6
Top 5 Classes	16,854	61
All Others	10,865	39

Total Cases = 27,719 = 100%

Table 13. Top Five Ranked Therapeutic Classes by Type of Case

			Top 5 Therapeutic Classes				
			Rank				
Type of Case	N	%	1	2	3	4	5
Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes	2,406	9	CNS	CV	INF	STV	HORM
All Other Manufacturer Cases	13,119	47	CNS	CV	INF	DX	SKIN
Direct, Health Professional Cases	1,759	6	CNS	INF	CV	STV	DX

Total Cases = 27,719 = 100%

Table 14. Top Five Ranked Therapeutic Classes by Type of Outcome

			Top 5 Therapeutic Classes				
			Rank				
Type of Outcome	N	%	1	2	3	4	5
Death	826	3	CNS	CV	INF	NEO	STV
Hosp Only	2,700	10	CNS	CV	INF	HORM	DX
Other Outcomes	13,328	48	CNS	CV	INF	DX	SKIN

Total Cases = 27,719 = 100%

Table 15. Top Five Ranked Therapeutic Classes by Type of Case and Outcome

			Top 5 Therapeutic Classes				
			Rank				
	N	%	1	2	3	4	5
Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes							
Death	465	2	CNS	CV	INF	STV	NEO
Hosp Only	889	3	CNS	CV	INF	HORM	SKIN
Other Outcomes	1,052	4	CNS	STV	CV	INF	HORM
All Other Manufacturer Cases							
Death	240	1	CV	INF	CNS	NEO	DX
Hosp Only	1,440	5	CNS	CV	INF	HORM	DX
Other Outcomes	11,439	41	CNS	CV	INF	DX	SKIN
Direct, Health Professional Cases							
Death	136	*	NEO	CV	CNS	INF	STV
Hosp Only	443	2	CNS	INF	CV	NEO	DX
Other Outcomes	1,180	4	CNS	INF	CV	STV	DX

Total Cases= 27,719 = 100%

Interval between Suspect Drug/Biologic Initiation and Adverse Reaction Onset

During 1986, about 40% (n=12,090) of the within-scope cases listed both the date of suspect drug/biologic initiation and the date of AR onset (Figure 10). This section of the analyses uses 12,090 as the denominator. Tables 16-18 give an overview of these cases by type of case, outcome, and crossclassified by case and outcome.

A comparison of the frequency distribution in Table 16 with that in Figure 2 shows a difference in the distribution of cases by type of case. Direct cases represented 17% of the cases listing both dates while they accounted for only about 9% of the total cases.

Additionally, a comparison of the frequency distribution in Table 17 with that of Figure 3 depicts a difference in distributions by type of outcome. Dead and hospitalized cases represented about one-fifth of all cases while they represented about one-quarter of the cases containing both dates.

Crossclassification of the data is presented in Table 18. Here, a little over one-half of the cases were "all other manufacturer" cases containing "other outcomes." This was lower than the respective proportion of two-thirds for all cases, found in Table 1.

Figure 11 shows that about two-fifths of ARs occurred within one day of initial drug/biologic administration, and 90% occurred within six months. Tables 19-21 and Figures 12-13 present these data stratified by type of case, outcome, and crossclassified by case and outcome. Note that in Table 19, about one-third of these cases were "all other manufacturer" cases for "≤1" day." A greater percentage of the direct cases (74%), as compared to the manufacturer cases (63%), reported intervals of ≤2 weeks, whereas a greater percentage of the manufacturer cases (37%), as compared to the direct cases (26%), reported intervals of >2 weeks. Table 20 shows that the outcome of death occurred about evenly among the "≤1," "2-14," and "15-182" day intervals. Table 21 shows that about one-quarter of the cases were for "all other manufacturer" with "other outcome" cases in the "≤1 day" interval.

Figure 10: Distribution of Cases by Interval Between Drug/Biologic Initiation and AR Onset
n=29,926 (100%)

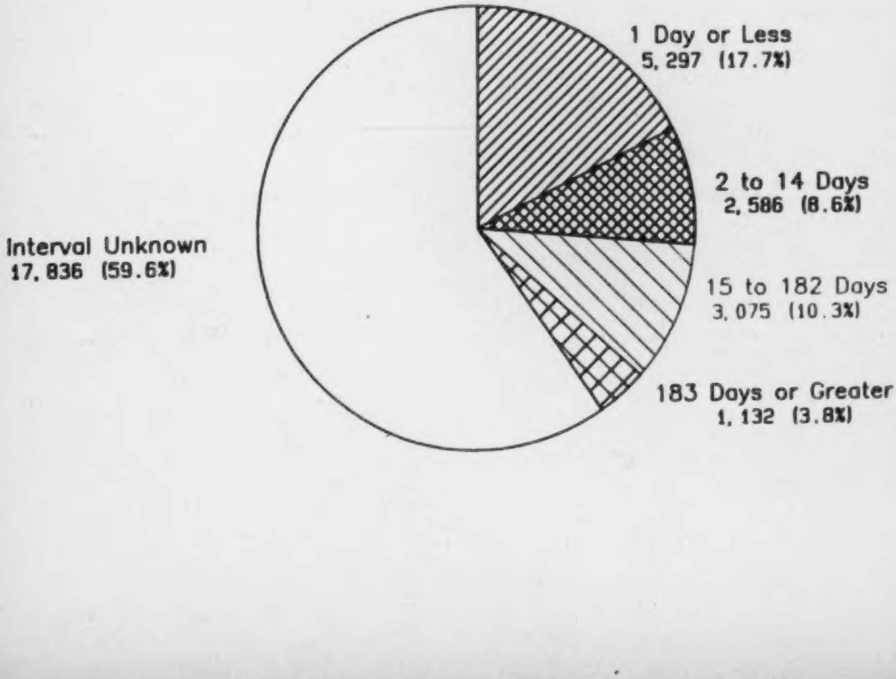


Table 16. Distribution of Cases Having Both Drug/Biologic Start Date and AR Onset Date by Type of Case

Type of Case					
Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes		All Other Manufacturer Cases		Direct, Health Professional Cases	
N	%	N	%	N	%
2,011	17	7,996	66	2,083	17

Total Cases = 12,090 = 100%

Table 17. Distribution of Cases Having Both Drug/Biologic Start Date and AR Onset Date by Type of Outcome

Type of Outcome					
Death		Hospitalization		Other Outcomes	
N	%	N	%	N	%
692	6	2,448	20	8,950	74

Total Cases = 12,090 = 100%

Table 18. Distribution of Cases Having Both Drug/Biologic Start Date and AR Onset Date by Type of Case and Outcome

	Type of Case					
	Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes		All Other Manufacturer Cases		Direct, Health Professional Cases	
Type of Outcome	N	%	N	%	N	%
Death	365	3	202	2	125	1
Hospitalization	806	7	1,126	9	516	4
Other Outcomes	840	7	6,668	55	1,442	12

Total Cases = 12,090 = 100%

Table 19. Distribution of Cases by Interval Between Drug/Biologic Initiation and AR Onset and Type of Case

	Type of Case					
	Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes		All Other Manufacturer Cases		Direct, Health Professional Cases	
Interval (days)	N	%	N	%	N	%
≤ 1	706	6	3,602	30	989	8
2-14	450	4	1,579	13	557	5
15-182	562	5	2,100	17	413	3
≥ 183	293	2	715	6	124	1

Total Cases= 12,090 - 100%

Figure 11: Distribution of Cases by Interval Between Drug/Biologic Initiation and AR Onset

n=12,090 (100%)

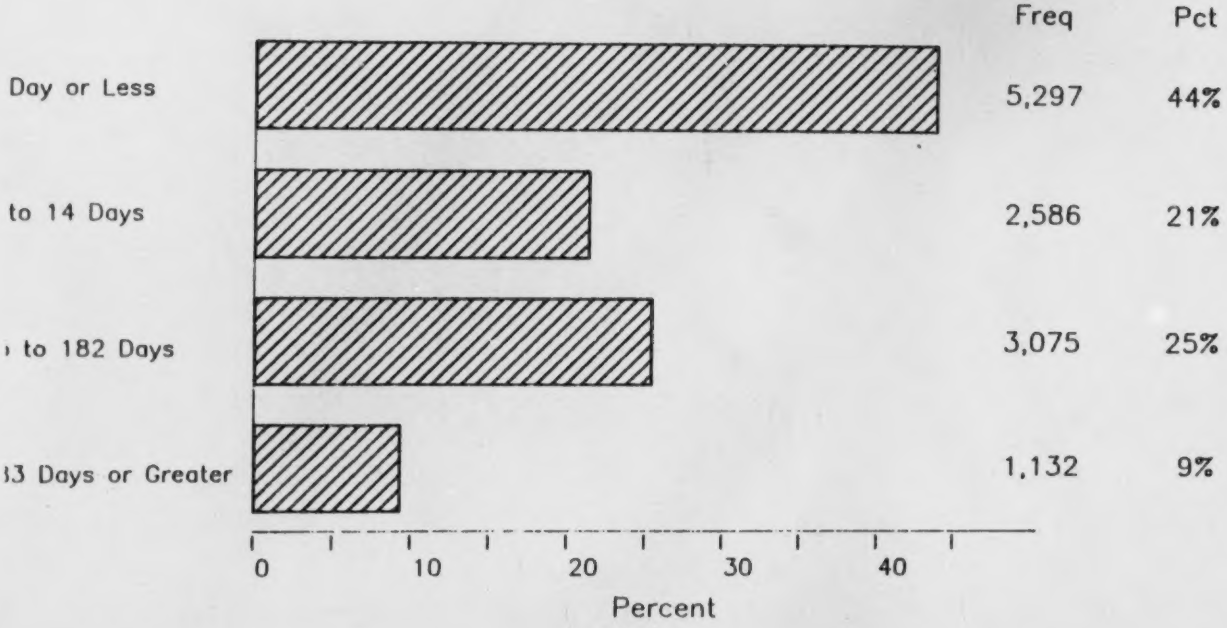


Figure 12: Distribution of Cases by Interval Between Drug/Biologic Initiation & AR Onset and Type of Case

n=12,090 (100%)

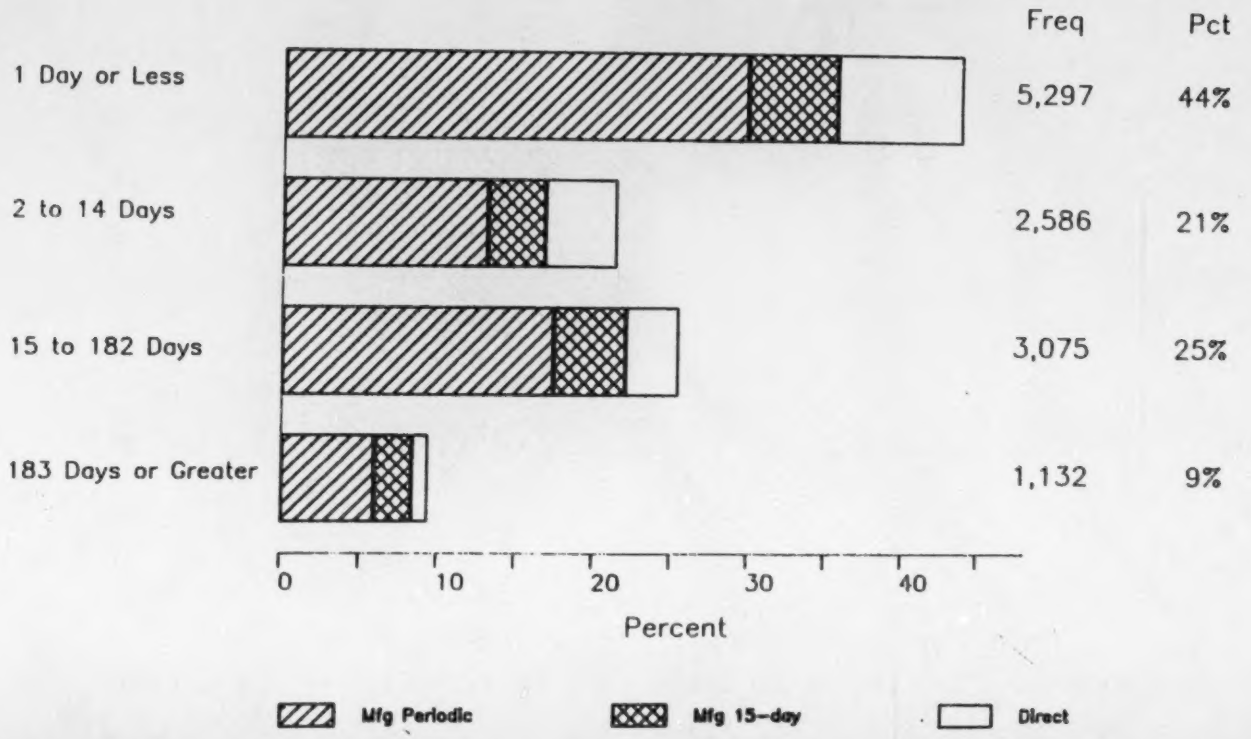


Figure 13: Distribution of Cases by Interval Between Drug/Biologic Initiation & AR Onset and Outcome

n=12,090 (100%)

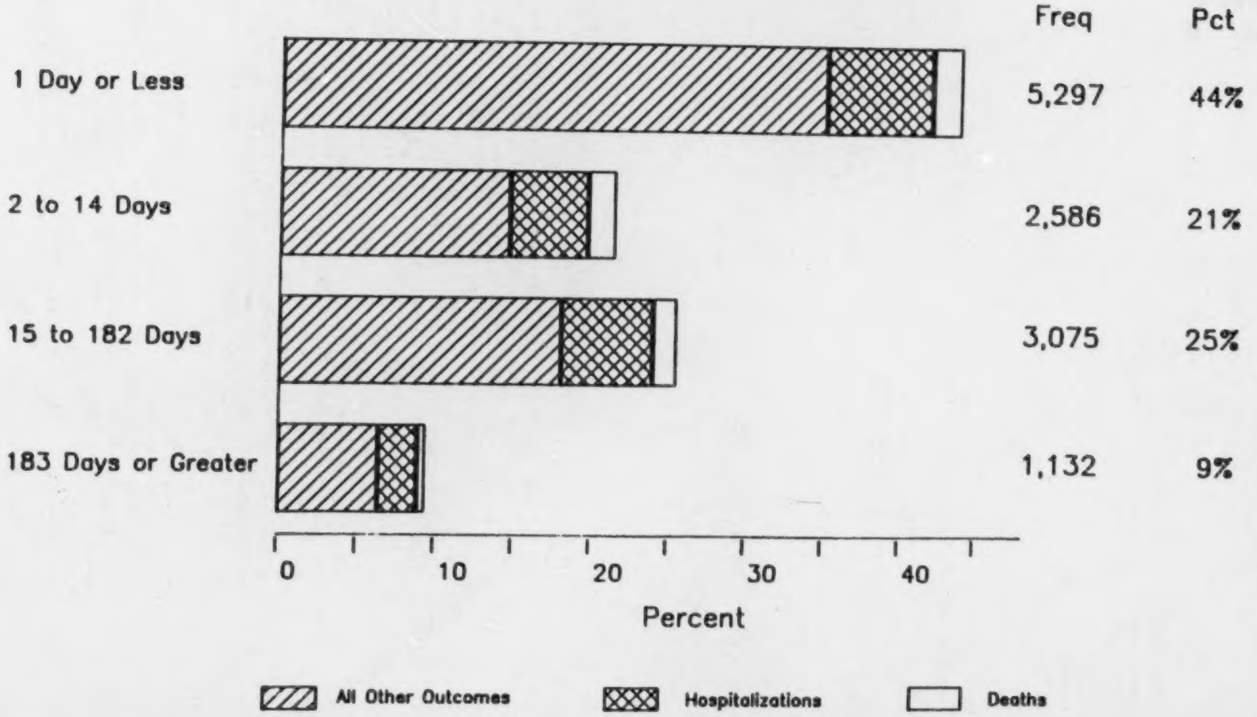


Table 20. Distribution of Cases by Interval Between Drug/Biologic Initiation and AR Onset and Type of Outcome

	Type of Outcome					
	Death		Hospitalization		Other Outcomes	
Interval (days)	N	%	N	%	N	%
≤1	232	2	835	7	4,230	35
2-14	213	2	602	5	1,771	15
15-182	185	2	710	6	2,180	18
≥183	62	1	301	2	769	6

Total Cases= 12,090 = 100%

Table 21. Distribution of Cases by Interval Between Drug/Biologic Initiation and AR Onset and Type of Case and Outcome

	Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes						All Other Manufacturer Cases						Direct, Health Professional Cases					
	Death		Hosp		Other		Death		Hosp		Other		Death		Hosp		Other	
Interval (days)	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
≤1	129	1	227	2	350	3	76	1	395	3	3,131	26	27	*	213	2	749	6
2-14	118	1	178	1	154	1	60	*	262	2	1,257	10	35	*	162	1	360	3
15-182	85	1	261	2	216	2	54	*	333	3	1,713	14	46	*	116	1	251	2
≥183	33	*	140	1	120	1	12	*	136	1	567	5	17	*	25	*	82	1

Total Cases= 12,090 = 100%

Patient Sex

In 1986, about 75% (n=22,514) of the within-scope cases had the patient's sex reported (Figure 14). In this section, 22,514 is used as the denominator. For the manufacturer cases having nonlabeled ARs and serious outcomes, the percent of cases reporting sex was higher (87%) than the overall percentage; for all other manufacturer cases, it was lower (70%); and for direct, health professional cases, it was much higher (97%). With respect to type of outcome, for cases involving death or hospitalization, the percent was higher (88% and 93%, respectively) than overall; for other outcomes, it was slightly lower (71%).

Tables 22-24 give an overview of these cases by type of case, outcome, and crossclassified by case and outcome. These distributions of cases are quite similar to the overall distributions of cases in Figures 2-3 and Table 1. There are, however, two noteworthy differences in the 1986 data compared to the 1985 data: (1) the percentage of manufacturer cases having nonlabeled ARs and serious outcomes with sex information decreased from 25% in 1985 to 17% in 1986; (2) the "all other manufacturer" cases having this information increased from 63% to 71%, respectively.

Of the cases which included patient sex, 58% were female (see Figure 15). Tables 25-27 and Figures 16-17 present the distribution of cases by sex and type of case and outcome and crossclassified by case and outcome. Table 25 shows that for the "manufacturer cases involving nonlabeled ARs and serious outcomes," the proportion of females and males was about equal, Table 26 notes that this also holds true for cases having outcomes of death or hospitalization. Table 27 shows that the biggest difference in the distribution of females and males occurred in the "all other manufacturer" with "other outcome" cases stratum.

Figure 14: Distribution of Cases by Sex

.n=29,926 (100%)

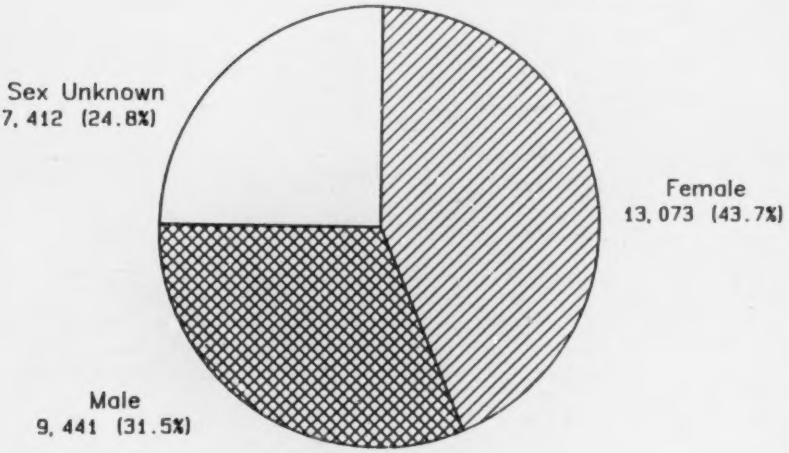


Table 22. Distribution of Cases with Known Patient Sex by Type of Case

Type of Case					
Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes		All Other Manufacturer Cases		Direct, Health Professional Cases	
N	%	N	%	N	%
3,828	17	15,981	71	2,705	12

Total Cases= 22,514 = 100%

Table 23. Distribution of Cases with Known Patient Sex by Type of Outcome

Type of Outcome					
Death		Hospitalization		Other Outcomes	
N	%	N	%	N	%
1,187	5	4,171	19	17,156	76

Total Cases= 22,514 = 100%

Table 24. Distribution of Cases with Known Patient Sex by Type of Case and Outcome

	Type of Case					
	Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes		All Other Manufacturer Cases		Direct, Health Professional Cases	
Type of Outcome	N	%	N	%	N	%
Death	686	3	327	1	174	1
Hospitalization	1,478	7	2,011	9	682	3
Other Outcomes	1,664	7	13,643	61	1,849	8

Total Cases= 22,514 = 100%

Figure 15: Distribution of Cases by Sex

n=22, 514 (100%).

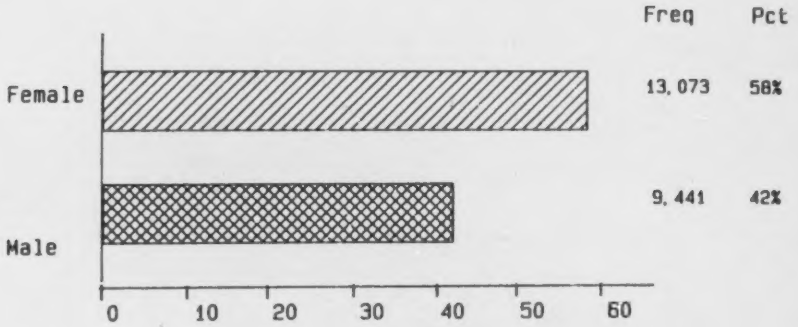


Figure 16: Distribution of Cases by Sex and Type of Case

n=22,514 (100%)

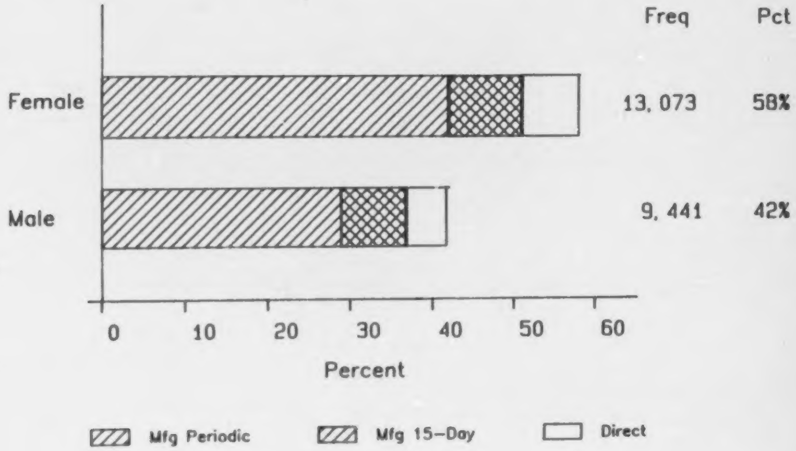


Table 25. Distribution of Cases by Sex and Type of Case

Sex	Type of Case Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes N	%	All Other Manufacturer Cases N	%	Direct, Health Professional Cases N	%
Female	2,136	9	9,383	42	1,554	7
Male	1,692	8	6,598	29	1,151	5

Total Cases= 22,514 = 100%

Table 26. Distribution of Cases by Sex and Type of Outcome

Sex	Type of Outcome Death N	%	Hospitalization N	%	Other Outcomes N	%
Female	578	3	2,350	10	10,145	45
Male	609	3	1,821	8	7,011	31

Total Cases= 22,514 = 100%

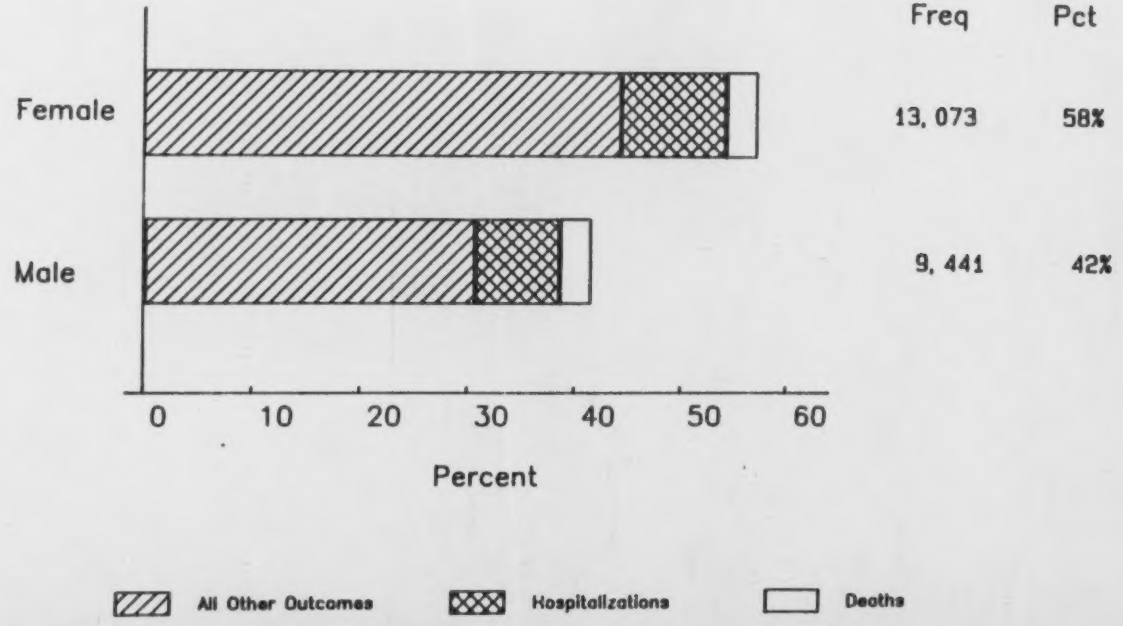
Table 27. Distribution of Cases by Sex and Type of Case and Outcome

	Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes						All Other Manufacturer Cases						Direct, Health Professional Cases					
	Death		Hosp		Other		Death		Hosp		Other		Death		Hosp		Other	
Sex	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Female	340	2	810	4	986	4	157	1	1,171	5	8,055	36	81	*	369	2	1,104	5
Male	346	2	668	3	678	3	170	1	840	4	5,588	25	93	*	313	1	745	3

Total Cases= 22,514 = 100%

Figure 17: Distribution of Cases by Sex and Outcome

n=22,514 (100%)



Patient Age

Of the within-scope cases, 62% (n=18,550) reported patient age (Figure 18). In this section, 18,550 is the denominator. Among the "manufacturer cases having nonlabeled ARs and serious outcomes," 76% included patient age; for "all other manufacturer" cases, it was 56%; and for "direct, health professional" cases, it was much higher at 91%. With respect to type of outcome, for cases reporting death or hospitalization, this percent was higher than the overall rate, 78% and 83%, respectively; for other outcomes, it was 57%.

Tables 28-30 give an overview of these cases by type of case, outcome, and crossclassified by case and outcome. They were generally quite similar in respective distributions of cases as per Figures 2-3 and Table 1. However, note that "all other manufacturer" cases with "other outcomes" made up 57% of cases with known patient age compared to 67% of all within-scope cases.

Of the cases reporting patient age, nearly one-third were in the " ≥ 60 years" stratum (see Table 31), and only one-sixth of cases were in the " ≤19 years" stratum. Overall, the median age was 45 years (interquartile range:28-63 years). Tables 32-34 present the distribution of cases by age category and type of case, and outcome and crossclassified by case and outcome.

Type of Case

"15-Day" Cases. Table 32 shows that a little over one-third of the "manufacturer cases having nonlabeled ARs and serious outcomes" ("15-day" cases) were accounted for by those " ≥ 60 years"--about the same proportion as overall (see Table 31). The median age for this type of case was 47 years (interquartile range:26-65 years).

"Periodic" Cases. Table 32 notes a similar ordering of the four age strata among the "periodic" cases as in the "15-day" cases, with the " ≥ 60 years" stratum ranked first, "20-39 years" stratum second, "40-59 years" stratum third, and " ≤ 19 years" stratum last. However, these cases were more evenly distributed among the three older age strata than the "15-day" cases. The median age for this type of case was 43 years (interquartile range:28-62 years).

"Direct" Cases. Again referring to Table 32, the distribution of "direct, health professional" cases across the age intervals was very similar to the respective distribution for the "15-day" cases. Again, the rank order of percentage of cases among the age intervals was the same as for the other types of cases. The median age here was 48 years (interquartile range:28-65 years).

Figure 19 displays age information in 20 five-year age intervals (by the midpoint of the interval), stratified by type of case.

Figure 18: Distribution of Cases by Age

n=29,926 (100%)

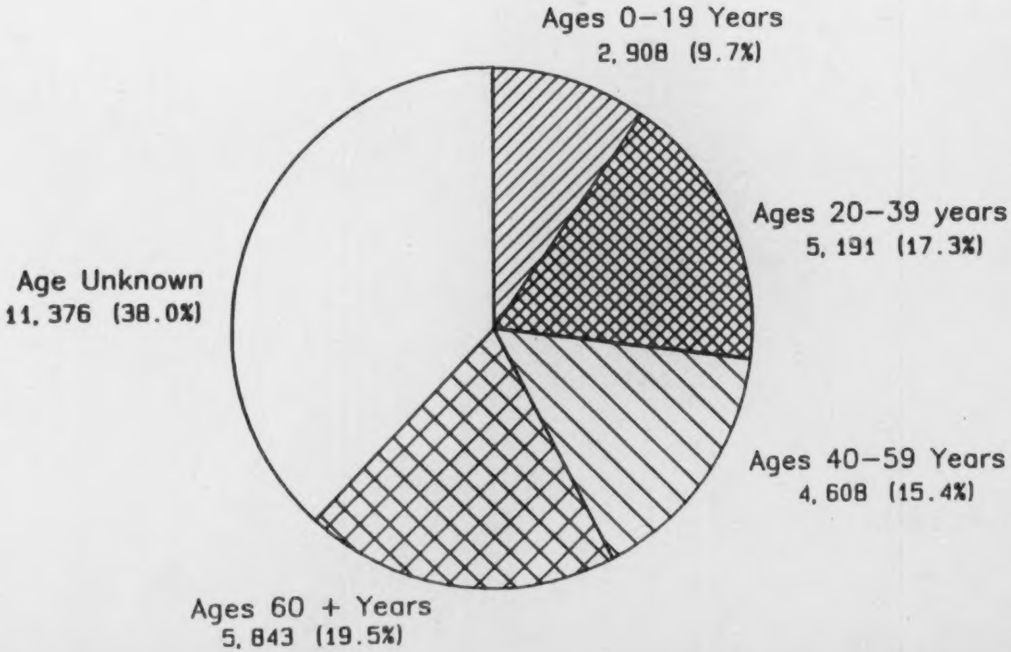


Table 28. Distribution of Cases with Known Patient Age by Type of Case

Type of Case

Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes		All Other Manufacturer Cases		Direct, Health Professional Cases	
N	%	N	%	N	%
3,317	18	12,691	68	2,542	14

Total Cases= 18,550 = 100%

Table 29. Distribution of Cases with Known Patient Age by Type of Outcome

Type of Outcome

Death		Hospitalization		Other Outcomes	
N	%	N	%	N	%
1,048	6	3,719	20	13,783	74

Total Cases= 18,550 = 100%

Table 30. Distribution of Cases with Known Patient Age by Type of Case and Outcome

Type of Case

	Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes		All Other Manufacturer Cases		Direct, Health Professional Cases	
Type of Outcome	N	%	N	%	N	%
Death	598	3	285	2	165	1
Hospitalization	1,294	7	1,775	10	650	4
Other Outcomes	1,425	8	10,631	57	1,727	9

Total Cases= 18,550 = 100%

Table 31. Distribution of Cases by Age Interval

Age Interval (years)	N	%
≤19	2,908	16
20-39	5,191	28
40-59	4,608	25
≥60	5,843	31

Total Cases= 18,550 = 100%

Table 32. Distribution of Cases by Age Interval and Type of Case

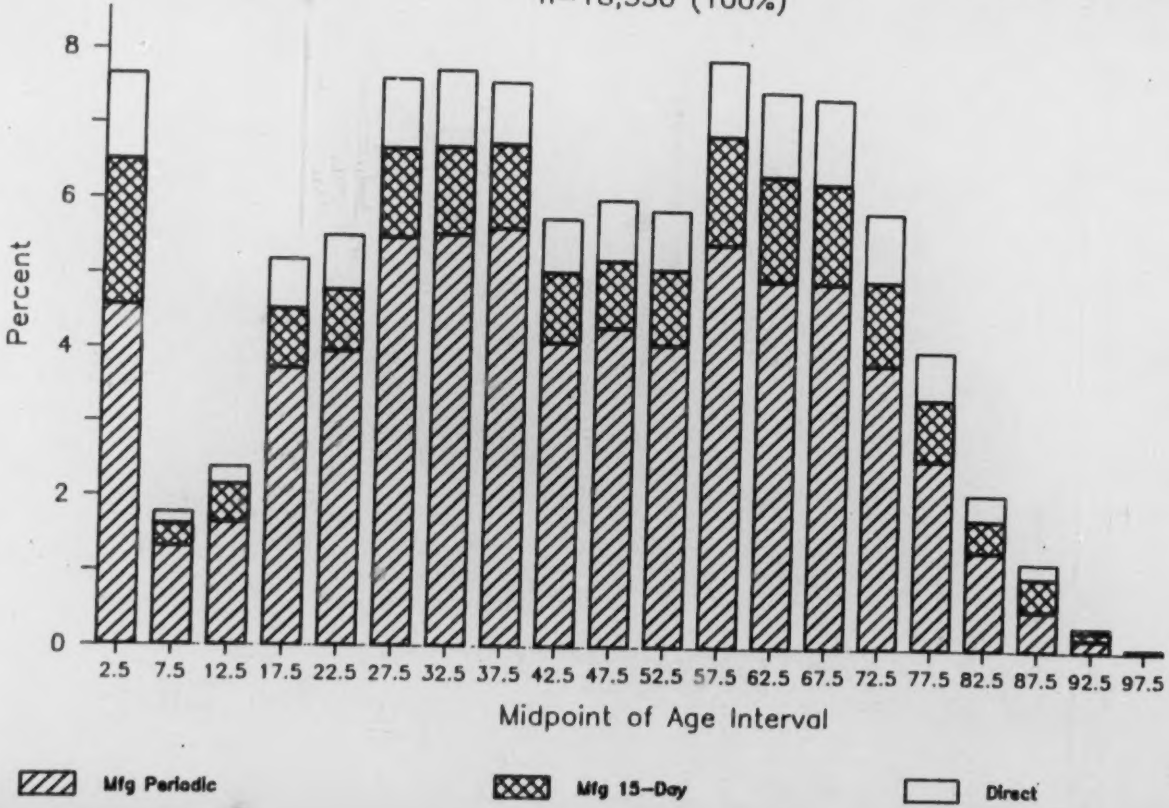
Type of Case

Age Interval (years)	Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes		All Other Manufacturer Cases		Direct, Health Professional Cases	
	N	%	N	%	N	%
≤19	621	3	1,904	10	383	2
20-39	779	4	3,745	20	667	4
40-59	753	4	3,247	18	608	3
≥60	1,164	6	3,795	20	884	5

Total Cases= 18,550 = 100%

Figure 19: Distribution of Cases by Age and Type of Case

n=18,550 (100%)



Type of Outcome

Death. Table 33 shows that the "≥60 year" stratum was associated with the highest percentage of death outcomes; 51% of AR cases with death listed were for this group. The median age for cases mentioning death was 60 years (interquartile range:36-72 years).

Hospitalization. Again, Table 33 shows that those in the "≥60 year" stratum were associated with the highest percentage of hospitalization cases; 39% (1,466/3,719) of cases which listed hospitalization were in this stratum. The median age for hospitalization cases was 52 years (interquartile range:30-67 years); this median age was about eight years lower than for cases reporting death.

Other Outcomes. As shown in Table 33, the distribution of age for cases in the "other outcomes" stratum was quite different from the respective age distributions among cases reporting death or hospitalization. A noticeably higher proportion of cases in the death and hospitalization strata was in the oldest age category, "≥60," while in the "other outcome" group, cases were more evenly distributed between three age categories: "20-39," "40-59," and "≥ 60." Thus, the median age for the "other outcomes" group was much lower at 41 years (interquartile range: 26-61).

Figure 20 graphically presents age distribution stratified by outcome.

Type of Case by Type of Outcome

Table 34 shows the distribution of age by type of case crossclassified by type of outcome. Not suprisingly, a little over one-half (57%) of the "manufacturer cases having nonlabeled ARs and serious outcomes" group reported death or hospitalization. The respective percentages for "all other manufacturer" cases and "direct, health professional" cases were 16% and 32%.

Table 33. Distribution of Cases by Age Interval and Type of Outcome

Type of Outcome

Age Interval (years)	Death N	Death %	Hospitalization N	Hospitalization %	Other Outcomes N	Other Outcomes %
≤19	125	1	487	3	2,296	12
20-39	156	1	878	5	4,157	22
40-59	237	1	889	5	3,482	19
≥60	530	3	1,465	8	3,848	21

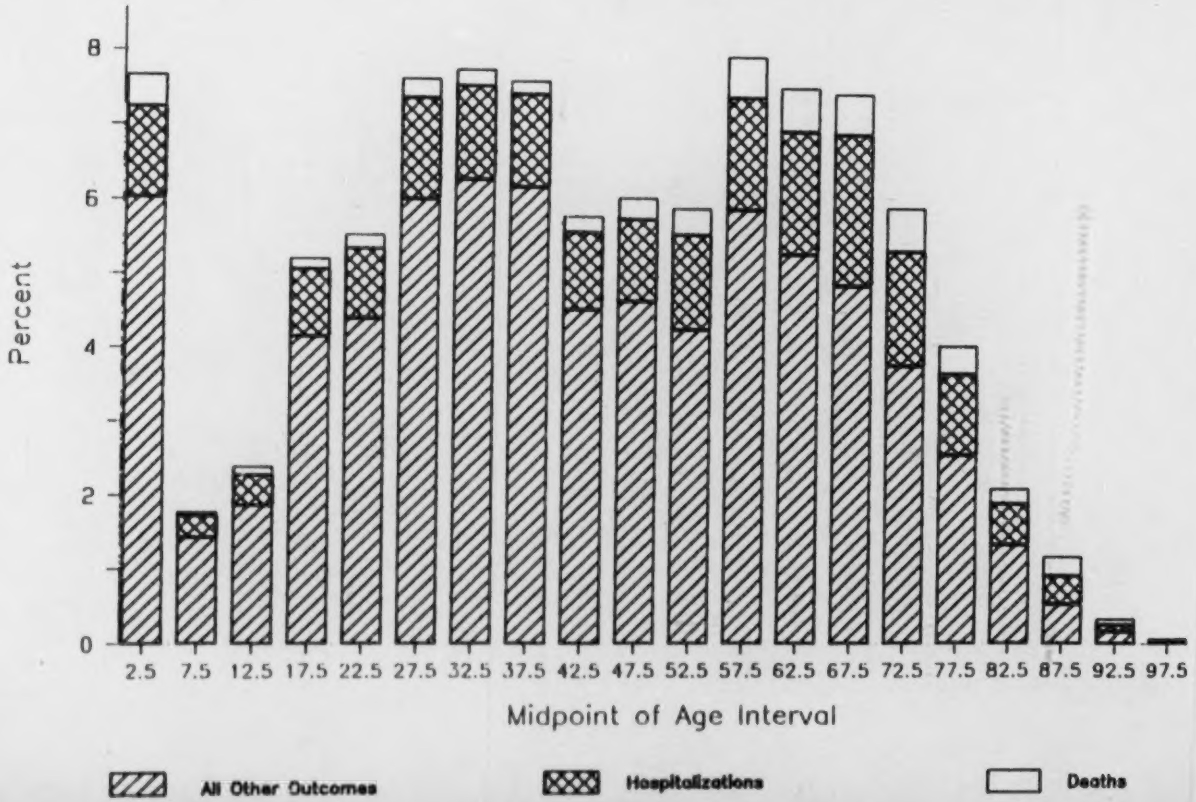
Total Cases= 18,550 = 100%

Table 34. Distribution of Cases by Age Interval and Type of Case and Outcome

	Manufacturer Cases Containing Nonlabeled ARs and Serious Outcomes						All Other Manufacturer Cases						Direct, Health Professional Cases					
Age Interval (years)	Death N	Death %	Hosp N	Hosp %	Other N	Other %	Death N	Death %	Hosp N	Hosp %	Other N	Other %	Death N	Death %	Hosp N	Hosp %	Other N	Other %
≤ 19	91	*	199	1	331	2	22	*	213	1	1,669	9	12	*	75	*	296	2
20-39	105	1	283	2	391	2	35	*	436	2	3,274	18	16	*	159	1	492	3
40-59	128	1	314	2	311	2	61	*	439	2	2,747	15	48	*	136	1	424	2
≥60	274	1	498	3	392	2	167	1	687	4	2,941	16	89	*	280	2	515	3

Total Cases= 18,550 = 100%

Figure 20: Distribution of Cases by Age and Outcome
n=18,550 (100%)



Patient Age by Sex

Both age and sex were listed for 61% (n=18,177) of within-scope cases (Figure 21). Thus, 18,177 is the denominator for analyses in this section. Of these, 57% were female, which is almost identical to the overall rate of 58% female. Table 35 shows the distribution of cases by age and sex; the distributions are somewhat different from the distribution of cases with age information only (Table 31).

For the females with information on age, the median age was 43 years (interquartile range:29-63 years) while for males, the median age was 47 years (interquartile range:27-64 years). Figure 22 summarizes the age by sex data. Also of interest is that for most five-year age groups, the proportion of females was greater than males (Figure 23). The exceptions were the three youngest ages (midpoints 2.5, 7.5, and 12.5), where there were more males than females, and for two age groups (midpoints 17.5 and 62.5) where there were roughly equal proportions of females and males.

Table 35. Distribution of Cases by Age Intervals and Sex

Sex/Age Interval (years)	N	%
All	18,177	100
Female	10,414	57
≤19	1,284	7
20-39	3,380	19
40-59	2,604	14
≥60	3,146	17
Male	7,763	43
≤19	1,449	8
20-39	1,757	10
40-59	1,963	11
≥60	2,594	14

Figure 21: Distribution of Cases by Age and Sex
n=29,926 (100%)

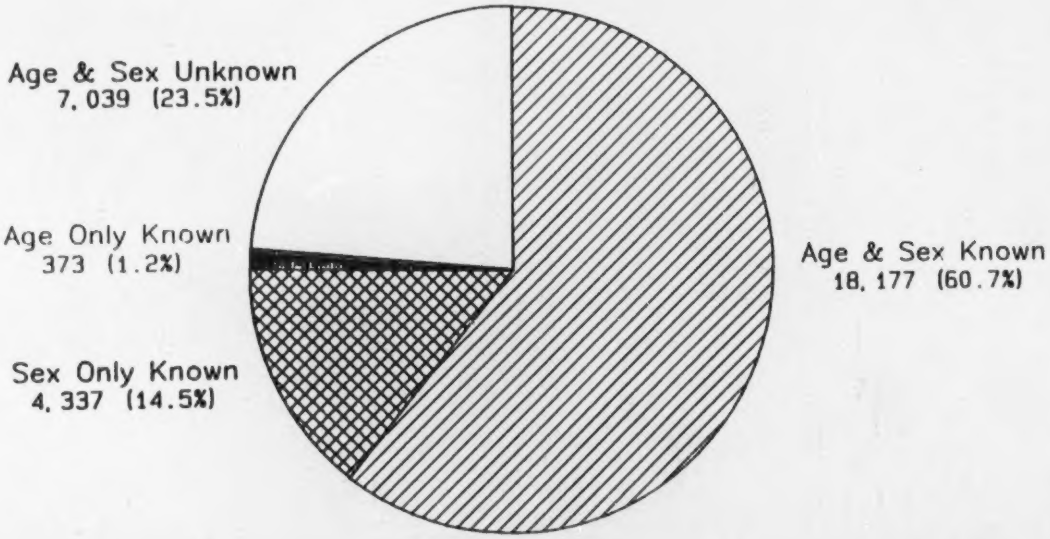


Figure 22: Distribution of Cases by Age and Sex

n=18,177 (100%)

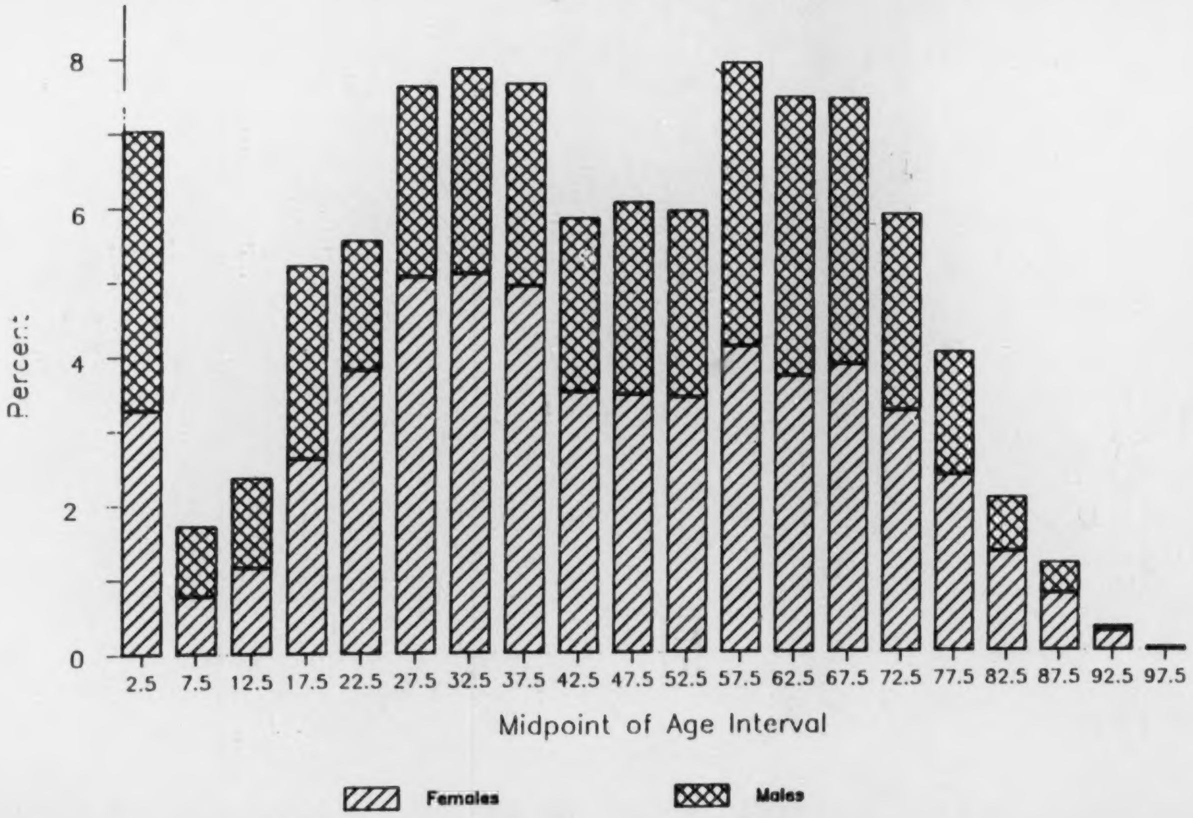
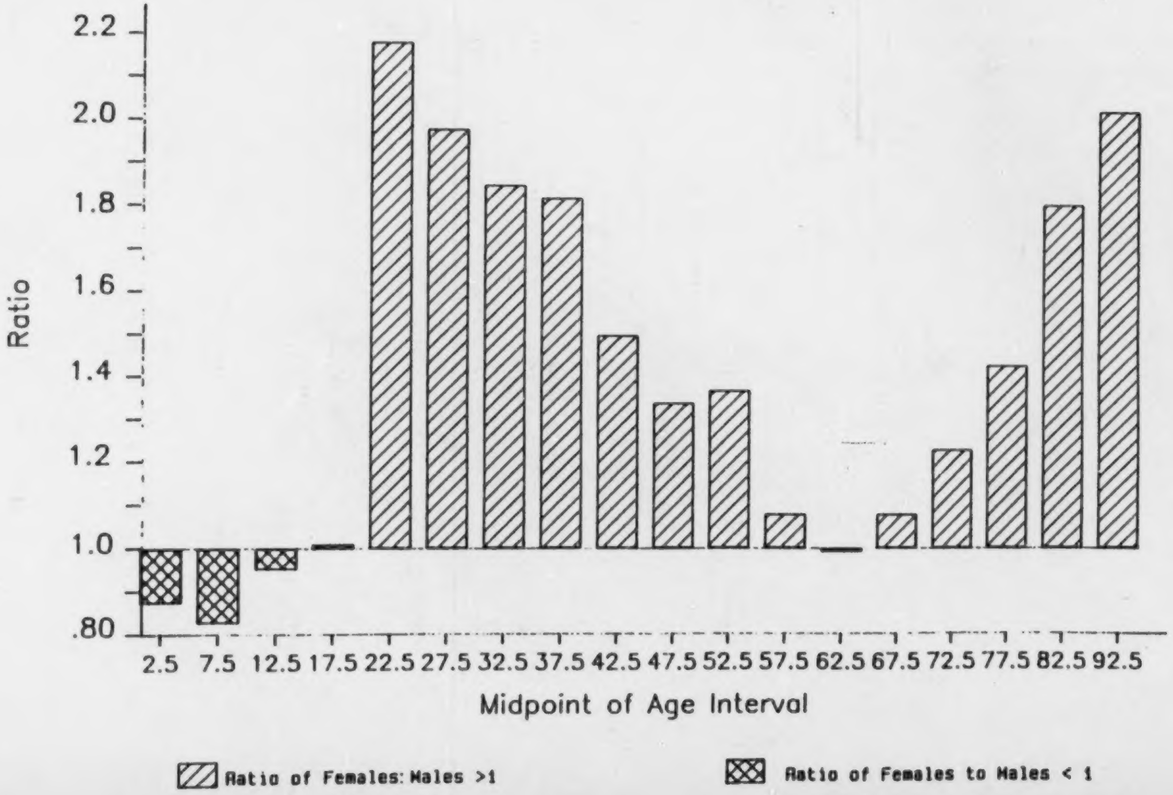


Figure 23: Ratio of Females to Males by Age



DISCUSSION

There were 29,926 cases received and computerized by FDA in 1986 which were evaluable, domestic, spontaneous reports received either directly from health professionals or indirectly from health professionals via pharmaceutical manufacturers. These cases contained information on adverse reactions (ARs) to marketed drugs or biologics which had been administered within therapeutic dosage ranges. The following discussion is limited to these cases.

In both 1985 and 1986, cases from manufacturers accounted for about 90% of the aforementioned cases. Also in both years, about one-fifth of the cases had reported outcomes of death or hospitalization. Again in both years, about one-half of the cases involved the following body systems: "body as a whole," "skin and appendages," and "nervous." In both 1985 and 1986, about 40% of cases had dechallenge information, and a little less than 10% had rechallenge data.

In both 1985 and 1986, there were 69 new chemical or biological entities (NCBEs) which had been approved and first marketed within three years of the analysis year and which are still marketed at the time of the analyses. In both years, about one-fifth of the cases involved a suspect drug/biologic which was a NCBE.

In 1986, the Top Five ranked therapeutic classes in terms of overall number of cases were: central nervous system agents, cardiovascular drugs, anti-infective agents, diagnostic agents, and hormones and synthetic substitutes.

In 1986, a higher proportion of cases had complete dates for suspect drug/biologic initiation and AR onset compared to 1985 (40% versus 35%). In both years, a little less than two-thirds of cases had ARs which started within two weeks of drug/biologic initiation.

There was a 5% decrease in the number of the cases in 1986 which listed sex compared to 1985 (75% versus 80%). However, in both years, about 58% of these cases were female.

About 60% of the cases for 1985 and 1986 listed age. In both years, nearly one-third of cases were 60 years of age or older.

Although the percentage of "direct, health professional" ("direct") cases was small in both years, these reports were more complete on "key" items necessary for AR interpretation. For 1986 cases, the following comparisons regarding the completeness of cases were made between direct and manufacturer cases:

1. Dechallenge data: 49% of direct cases versus 39% of manufacturer cases had these data.
2. Rechallenge data: 16% of direct cases versus 8% of manufacturer cases had these data.
3. Sex information: 97% of direct cases versus 73% of manufacturer cases had this information.
4. Age information: 91% of direct cases versus 59% of manufacturer cases had this information.
5. Suspect drug/biologic initiation and AR date information: 74% of

APPENDIX I

PRIMARY CATEGORIES

HIERARCHICAL BODY-SYSTEM CLASSIFICATION

I Body as a Whole
II Cardiovascular System
III Digestive System
IV Endocrine System
V Hemic and Lymphatic Sysem
VI Metabolic and Nutritional Disorders
VII Musculoskeletal System
VIII Nervous System
IX Respiratory System
X Skin and Appendages
XI Special Senses
XII Urogenital System

Categories and Subcategories	Coding Symbol
I. Body as a Whole	BODY/GEN
A. General, Functional and NEC	
B. Regional and NEC	
1. Head - includes:	BODY/HEAD
a. face b. scalp excludes: special senses	
2. Neck - includes:	BODY/NECK
a. cervical spine	
3. Thorax - includes:	BODY/THOR
a. axilla b. chest c. intercostal d. mediastinal e. precordial f. substernal	
4. Abdomen - includes:	BODY/ABDO
a. epigastrium b. intraperitoneal c. inguinal d. mesenteric e. peritoneal cavity f. retroperitoneal g. umbilical	
5. Pelvic - includes:	BODY/PELV
a. intrapelvic b. perineum c. suprapubic	
6. Back - includes:	BODY/BACK
a. dorsal b. flank c. lumbosacral d. sacroiliac	
7. Upper Extremity - includes:	BODY/UE
a. deltoid b. shoulder joint	
8. Lower Extremity - includes:	BODY/LE
a. hip joint	
9. Multiple Organ Syndromes NEC	BODY/MULT

II. Cardiovascular System	
A. General and NEC	CV/GEN
B. Cardiac Disorders	CV/CARD
1. General, Functional and NEC	CV/CARD/GEN
2. Endocardial Disorders	CV/CARD/END
3. Myocardial Disorders	CV/CARD/MYO
4. Pericardial Disorders	CV/CARD/PER
5. Coronary Vessel Disorders	CV/CARD/COR
6. Arrhythmias	CV/CARD/ARR
7. Conduction Abnormalities	CV/CARD/COND
C. Vascular Disorders	CV/VASC
1. General and NEC	CV/VASC/GEN
2. Arterial and Arteriolar Disorders	CV/VASC/ART
3. Venous and Venular Disorders	CV/VASC/VEN
4. Capillary Disorders	CV/VASC/CAP
5. Blood Pressure Disorders	CV/VASC/BP
III. Digestive System	
A. General, Functional and NEC	DIG/GEN
B. Regional	
1. Buccal Cavity - includes:	DIG/BUC
a. cheeks	
b. gums	
c. lips	
d. mouth	
e. palate	
f. teeth	
g. tongue	
2. Salivary Glands	DIG/SAL
3. Oropharynx (excludes nasopharynx)	DIG/OROP
4. Esophagus	DIG/ESOPH
5. Stomach	DIG/STOM
6. Duodenal	DIG/DUO
7. Gastro-Duodenal - includes:	DIG/GD
a. peptic	
8. Small Intestine - includes:	DIG/SI
a. jejunum	
b. ileum	
9. Colon	DIG/COL
10. Entercolon	DIG/EC
11. Rectum	DIG/REC
12. Anus	DIG/AN
13. Liver - includes:	DIG/LIV
a. parenchyma	
b. intrahepatic bile radicles	
14. Gall Bladder - includes:	DIG/GB
15. Pancrease - includes:	DIG/PAN
a. acinar tissue and pancreatic ducts (excludes insular tissue)	
IV. Endocrine System	ENDO/GEN
A. General, Polyglandular and NEC	
B. Specific Endocrine Glands	
1. Hypothalmaus	
2. Pituitary	ENDO/PIT
a. Anterior	ENDO/PIT/ANT
b. Posterior	ENDO/PIT/POST

3. Pineal	ENDO/PIN
4. Thyroid	ENDO/THYR
5. Parathyroid	ENDO/PARATHYR
6. Thymus	ENDO/THYM
7. Pancreas (endocrine only)	ENDO/PAN
8. Adrenal	ENDO/ADR
a. Cortex	ENDO/ADR/COR
b. Medulla	ENDO/ADR/MED
9. Gonads	
a. Testes	ENDO/TEST
b. Ovary	ENDO/OVAR
10. Placenta	ENDO/PLAC
11. Renal (endocrine only)- includes:	ENDO/REN
a. erythropoietin	
b. renin	
V. Hemic and Lymphatic System	
A. Hemic	
1. Hemic, General and NEC	HAL/GEN
a. Blood (viscosity and volume)	
b. Plasma	
c. Serum	
2. Erythrocyte Abnormalities, General and NEC	HAL/RBC/GEN
3. Erythrocyte Abnormalities specified as:	
a. hemoglobin disorders	HAL/RBC/HGB
b. erythrocytes increased	HAL/RBC/INC
c. erythrocytes decreased - includes: (i) anemias (NOS) (ii) anemias specified (iii) reticulocytopenia	HAL/RBC/DEC
4. Leukocyte Abnormalities, General and NEC	HAL/WBC/GEN
5. Leukocytes Abnormalities specified as	
a. leukocytes increased	HAL/WBC/INC
b. leukocytes decreased	HAL/WBC/DEC
6. Leukocyte Abnormalities specificed as to type:	
a. granulocytes increased	HAL/WBC/INC/G
b. granulocytes decreased	HAL/WBC/DEC/G
c. monocytes increased	HAL/WBC/INC/M
d. monocytes decreased	HAL/WBC/DEC/M
e. lymphocytes increased	HAL/WBC/INC/L
f. lymphocytes decreased	HAL/WBC/DEC/L
7. Thrombocyte Abnormalities (Platelets and Megakaryocytes) General and NEC	HAL/PLAT/GEN
8. Thrombocyte Abnormalities (Platelets or Megakaryocytes) specified as:	
a. increased	HAL/PLAT/INC
b. decreased	HAL/PLAT/DEC
9. Bone Marrow Abnormalities NEC	
a. marrow cells increased - includes: (i) myeloproliferative reactions not elsewhere classified	HAL/MAR/INC
b. marrow cells decreased -includes: (i) marrow depression NEC (ii) myelofibrosis (iii) pancytopenia	HAL/MAR/DEC
10. Coagulation Disorders, General and NEC - includes:	HAL/COAG/GEN

- a. bleeding time disorders NOS
- b. blood coagulation disorder NOS
- c. coagulation time disorder NOS
- d. hypercoagulability state

11. Coagulation Disorders specified as:

    - a. coagulation time increased (prolonged) or coagulation time decreased (shortened) HAL/COAG/CT
    - b. bleeding time increased (prolonged) or bleeding time decreased (shortened) HAL/COAG/BT
    - c. clot retraction increased (hastened) or clot retraction decreased (impaired) HAL/COAG/CR
    - d. capillary fragility (see cardiovascular system)
    - e. coagulation factor deficiencies and excesses (includes Factors I through XIII) HAL/COAG/CF
    - f. anticoagulant disorders - includes: HAL/COAG/AC
        - (i) disorders due to exogenous anti-coagulants

B. Lymphatic

1. Lymphatic Disorders, General and NEC HAL/LYM/GEN
2. Lymphatic Disorders specified as involving:
    - a. lymphatic vessels HAL/LYM/VES
    - b. lymphatic glands (nodes) HAL/LYM/GLN

C. Hemic and Lymphatic

1. Spleen Disorders HAL/SPLN
2. Reticulo-endothelial Disorders HAL/RE

VI. Metabolic and Nutritional Disorders

A. General and NEC MAN/GEN

1. Hypermetabolism (excludes hyperthyroidism)
2. Hypometabolism (excludes hypothyroidism)

B. Carbohydrate Disorders NEC MAN/CHO

1. Glycogen Disorders
2. Hyperglycemia
3. Hypoglycemia

C. Protein Disorders NEC MAN/PRO
D. Lipid Disorders MAN/LIP
E. Vitamin Disorders NEC MAN/VIT
F. Element and Ion Disorders NEC

1. Bromide Disorders MAN/ION/BR
2. Calcium Disorders - includes: MAN/ION/CA
    - a. hypercalcemia
    - b. hypocalcemia
3. Carbon Disorders MAN/ION/C
4. Chlorine Disorders MAN/ION/CL
5. Copper Disorder MAN/ION/CU
6. Fluorine Disorders MAN/ION/FL
7. Hydrogen Disorders MAN/ION/H
    - a. H ion increase (acidosis)
    - b. H ion decrease (alkalosis)
    - c. organic acid disorders NEC - includes:
        - (i) bile acides
        - (ii) citrates
        - (iii) ketoacids
        - (iv) lactate, etc.
8. Iodine Disorders MAN/ION/I
    - a. PBI
    - b. BEI
    - c. I^{131}

9. Iron Disorder	MAN/ION/FE
10. Magnesium Disorders	MAN/ION/MG
11. Manganese Disorders	MAN/ION/MN
12. Nitrogen Disorders - includes:	MAN/ION/N
a. amines	
b. amino acids	
c. ammonia (increase)	
d. BUN, urea (increase)	
e. creatine	
f. creatinine	
g. NPN (increase)	
h. uremia	
13. Oxygen Disorders - includes:	MAN/ION/O
a. anoxia	
b. hypoxia	
c. oxygen poisoning	
14. Phosphorus Disorders - includes:	MAN/ION/P
a. adenosine triphosphate	
15. Potassium Disorders - includes:	MAN/ION/K
a. hyperkalemia	
b. hypokalemia	
16. Sodium Disorders - includes:	MAN/ION/NA
a. hypernatremia	
b. hyponatremia	
17. Strontium Disorder	MAN/ION/SR
18. Sulfur Disorders	MAN/ION/S
19. Zinc Disorder	MAN/ION/ZN
G. Water Balance Disorders	MAN/WB
1. Dehydration	
2. Edema	
H. Pigment Disorders	MAN/PIG
1. Bilirubin Disorders	
2. Biliverdin Disorders	
3. Carotene Disorders	
4. Melanin Disorders	
5. Porphyria (excludes: hemoglobin, sulfhemoglobin, methemoglobin . . . see HAL/RBC/HGB)	
I. Purine Disorder	MAN/PUR
1. Pyrimidine	
2. Uric Acid (gout)	
3. Xanthine	
J. Enzyme Disorders NEC (code here those terms which cannot be coded as function tests or abnormalities specific to a primary system-organ category)	MAN/ENZ
K. Growth Disorders NEC (code here those terms which cannot be coded under endocrine)	MAN/GRO
L. Weight Disorders NEC	MAN/WT
M. Tissue Repair	MAN/TR
1. Healing Accelerated	
2. Healing Delayed	
3. Healing Impaired	
N. Inborn Errors of Metabolism NEC	MAN/IEM
1. Genetic	

VII. Musculo-skeletal System

A. Bone Disorders	
1. General and NEC	MS/BON/GEN
2. Bone Disorders Specified as Involving:	
a. cortex	MS/BON/COR
b. epiphysis	MS/BON/EPI
c. medulla (excluding hematopoietic marrow reactions)	MS/BON/MED
d. periosteum	MS/BON/PER
B. Bursal Disorders	MS/BUR
C. Cartilage Disorders	MS/CART
D. Fascial Disorders	MS/FAS
E. Joint Disorders - includes:	MS/JNT
1. Synovium	
F. Ligamentous Disorders	MS/LIG
G. Muscular Disorders	MS/MUS
H. Tendinous Disorders - includes:	MS/TEN
1. Tendon Sheath	

VIII. Nervous System

A. General and NEC	NER/GEN
B. Central Nervous System	NER/CNS
1. Brain	NER/CNS/B
2. Spinal Cord	NER/CNS/SC
3. Meninges	NER/CNS/M
4. Spinal Fluid	NER/CNS/CSF
C. Peripheral Nervous System	NER/PNS
1. Cranial Nerve Disorders	NER/PNS/CN
2. Spinal Nerve Disorders	NER/PNS/SN
D. Autonomic Nervous System	NER/ANS
1. Autonomic Ganglion Disorders	NER/ANS/GAN
2. Parasympathetic Disorders	NER/ANS/PSYM
a. parasympatholytic	NER/ANS/PSYM/L
b. parasympathomimetic	NER/ANS/PSYM/M
3. Sympathetic Disorders	NER/ANS/SYM
a. sympatholytic	NER/ANS/SYM/L
b. sympathomimetic	NER/ANS/SYM/M

IX. Respiratory System

A. General, Functional and NEC - includes:	RES/GEN
1. Specified Functional Disorders	
2. Abnormal Pulmonary Function Tests	
B. Nose - includes:	RES/NOSE
1. All Nasal Disorders Except Olfactory Sense (see Special Senses)	
C. Sinus - includes:	RES/SINS
1. Accessory Paranasal Sinuses	
D. Nasopharynx - includes:	RES/NASP
1. Eustachian Tube	
2. Tonsils (excludes oropharynx . . . see Digestive System)	

E. Larynx - includes:	RES/LRNX
1. Epiglottis	
2. Vocal Cords	
3. Voice	
F. Trachea	RES/TRAC
G. Bronchus and Bronchiole	RES/BRON
H. Lung - includes	RES/LUNG
1. Specified Morphological Disorders (excludes pulmonary function disorders)	
I. Pleura - includes:	RES/PLRA
1. Visceral Pleura	
2. Parietal Pleura	
3. Pleural Cavity	
4. Thoracic Cavity	
J. Diaphragm	RES/DPRM
X. Skin and Appendages	
A. General, Functional and NEC - includes:	SKIN/GEN
1. Pruritus Without Skin Eruption	
B. Dermatoses, General and NEC - includes:	SKIN/DERM/GEN
1. Angioedema	
2. Eczema	
3. Urticaria	
C. Dermatose Specified as:	SKIN/DERM/ERY
1. Erythema - includes:	
a. all common drug-induced maculopapular rashes	
b. erythema multiforme	
c. erythema nodosum	
d. exfoliative erythroderma	
e. discoid lupus erythematosus	
f. Stevens-Johnson syndrome	
2. Ulcerative-necrotic	SKIN/DERM/UN
a. epidermal necrolysis	
3. Vesiculo-bullous - includes:	SKIN/DERM/VB
a. dermatitis herpetiformis	
b. herpes simplex	
c. herpes zoster	
4. Hypertrophic - includes:	SKIN/DERM/HYP
a. fungoid (not fungal) dermatoses	
b. granulomatous dermatoses (NOS)	
c. ichthyosis	
d. keratosis	
e. lichenoid dermatoses	
f. lupoid dermatoses (other than discoid LE)	
g. neoplasia	
5. Acneform - includes:	SKIN/DERM/ACN
a. acne vulgaris	
b. pustular dermatoses	
6. Fungal (Mycotic)	SKIN/DERM/FUNG
7. Atrophic - includes:	SKIN/DERM/ATR
a. skin cicatrix	
b. skin striae	
8. Fixed Eruption	SKIN/DERM/FX
D. Sweat Gland Disorders - includes:	SKIN/SWGL

1. Miliaria
2. Sweating

E. Sebaceous Gland Disorders — SKIN/SBGL
F. Pigmentation Disorders — SKIN/PIG
G. Nail Disorders — SKIN/NAIL
H. Hair Disorders — SKIN/HAIR
I. Subcutaneous Disorders - includes: — SKIN/SUBQ

1. Injection Site Reactions

XI. Special Senses

A. Eye Disorders

1. General and NEC — SS/EYE/GEN
2. Vision Disorders NEC — SS/EYE/VIS
3. Eye Disorders Specified as Involving:

a. aqueous humor — SS/EYE/AH
b. conjunctiva — SS/EYE/CON
c. cornea — SS/EYE/COR
d. intraocular pressure — SS/EYE/IOP
e. lens — SS/EYE/LEN
f. optic nerve — SS/EYE/ON
g. retina — SS/EYE/RET
h. sclera — SS/EYE/SCL
i. uvea - includes: — SS/EYE/UVE
    (i) choroid
    (ii) ciliary body
    (iii) iris
    (iv) pupil

j. vitreous humor — SS/EYE/VH
k. eye appendages - includes: — SS/EYE/APP
    (i) eyelashes
    (ii) eyelids
    (iii) extraocular, oculomotor muscles
    (iv) lacrimal apparatus
    (v) tears

B. Ear Disorders

1. General and NEC — SS/EAR/GEN
2. Hearing Disorders NEC — SS/EAR/HER
3. Ear Disorders Specified as Involving:

a. external ear - includes: — SS/EAR/EXT
    (i) ear canal
b. middle ear - includes: — SS/EAR/MID
    (i) ear ossicles
    (ii) eardrum (excludes eustachian tube)
c. inner ear - includes: — SS/EAR/INN
    (i) cochlear nerve
    (ii) Meniere's syndrome (excludes vestibular apparatus . . . see Nervous System)

C. Smell Disorders (Olfactory Sense) — SS/SML
D. Taste Disorders (Gustatory Sense) — SS/TST

XII. Urogenital System

A. Urinary Tract Disorders — UG/UT

1. General, Functional and NEC — UG/UT/GEN
2. Kidney Disorders Specified as:

a. kidney morphologic — UG/UT/K/M
(Code morphologic and functional terms separately. If the reaction term includes both morphology and function, code under morphologic only)

Categories and Subcategories	Coding Symbol
b. kidney functional (Code reaction terms here which are functional and not secondary to a stated morphologic term)	UG/UT/K/F
c. ureter	UG/UT/URT
d. bladder morphologic (see comments under kidney morphologic)	UG/UT/B/M
e. bladder functional (see comments under kidney functional)	UG/UT/B/F
f. urethra	UG/UT/TA
g. urine abnormalities	UG/UT/URN
B. Female Genital Disorders	UG/FG
1. General and NEC	UG/FG/GEN
2. Organ Disorders Specified as Involving:	
a. ovary (excluding endocrine function)	UG/FG/OVA
b. fallopian tube	UG/FG/FT
c. uterus	UG/FG/UTRS
d. uterine cervix	UG/FG/UTCX
e. vagina	UG/FG/VAG
f. external genitalia	UG/FG/EXT
g. female breast	UG/FG/BRST
h. menstrual disorders	UG/FG/MENS
i. placental disorders	UG/FG/PLAC
j. pregnancy and puerperal disorders	UG/FG/PREG
k. menopausal disorders	UG/FG/MNPS
C. Male Genital Disorders	UG/MG
1. General and NEC	UG/MG/GEN
2. Organ Disorders Specified as Involving:	
a. epididymis	UG/MG/EPID
b. penis	UG/MG/PEN
c. prostate	UG/MG/PROS
d. scrotum	UG/MG/SCRT
e. seminal vesicles	UG/MG/SV
f. testis (excluding endocrine function)	UG/MG/TEST
g. male breast	UG/MG/BRST

From:
'COSTART' (Coding Symbols for Thesaurus of Adverse Reaction Terms). 2nd ed. Dept. of Health and Human Services, Food and Drug Administration, Center for Drugs and Biologics, Division of Drug and Biological Products Experience. 5600 Fishers Lane, Rockville, MD 20857. 1985.

Appendix 2: AHFS Pharmacologic-Therapeutic Classification

- 4:00 Antihistamine Drugs

- 8:00 Anti-Infective Agents
  - 8:04 Amebicides
  - 8:08 Anthelmintics
  - 8:12 Antibiotics
  - 8:16 Antituberculosis Agents
  - 8:18 Antivirals
  - 8:20 Antimalarial Agents
  - 8:24 Sulfonamides
  - 8:26 Sulfones
  - 8:28 Treponemicides
  - 8:32 Trichomonacides
  - 8:36 Urinary Anti-Infectives
  - 8:40 Miscellaneous Anti-Infectives

- 10:00 Antineoplastic Agents

- 12:00 Autonomic Drugs
  - 12:04 Parasympathomimetic (Cholinergic) Agents
  - 12:08 Anticholinergic Agents
  - 12:12 Sympathomimetic (Adrenergic) Agents
  - 12:16 Sympatholytic (Adrenergic Blocking) Agents
  - 12:20 Skeletal Muscle Relaxants
  - 12:92 Miscellaneous Autonomic Drugs

- 16:00 Blood Derivatives

- 20:00 Blood Formation and Coagulation
  - 20:04 Antianemia Drugs
  - 20:12 Coagulants and Anticoagulants
  - 20:40 Thrombolytic Agents

- 24:00 Cardiovascular Drugs
  - 24:04 Cardiac Drugs
  - 24:06 Antilipemic Agents
  - 24:08 Hypotensive Agents
  - 24:12 Vasodilating Agents
  - 24:16 Sclerosing Agents

- 28:00 Central Nervous System Agents
  - 28:04 General Anesthetics
  - 28:08 Analgesics and Antipyretics
  - 28:10 Opiate Antagonists
  - 28:12 Anticonvulsants
  - 28:16 Psychotherapeutic Agents
  - 28:20 Respiratory and Cerebral Stimulants
  - 28:24 Anxiolytics, Sedatives, and Hypnotics
  - 28:28 Antimanic Agents

- 32:00 Contraceptives (e.g., foams, devices)

- 34:00 Dental Agents

- 36:00 Diagnostic Agents
  - 36:04 Adrenocortical Insufficiency
  - 36:08 Amyloidosis
  - 36:12 Blood Volume
  - 36:16 Brucellosis
  - 36:18 Cardiac Function
  - 36:24 Circulation Time
  - 36:26 Diabetes Mellitus
  - 36:28 Diptheria
  - 36:30 Drug Hypersensitivity
  - 36:32 Fungi
  - 36:34 Gallbladder Function
  - 36:36 Gastric Function
  - 36:38 Intestinal Absorption
  - 36:40 Kidney Function
  - 36:44 Liver Function
  - 36:48 Lymphogranuloma Venereum
  - 36:52 Mumps

- 36:56 Myasthenia Gravis
- 36:60 Thyroid Function
- 36:61 Pancreatic Function
- 36:62 Phenylketonuria
- 36:64 Pheochromocytoma
- 36:66 Pituitary Function
- 36:68 Roentgenography
- 36:72 Scarlet Fever
- 36:76 Sweating
- 36:80 Trichinosis
- 36:84 Tuberculosis
- 36:88 Urine Contents

38:00 Disinfectants (for agents used on objects other than skin)

40:00 Electrolytic, Caloric, and Water Balance
- 40:04 Acidifying Agents
- 40:08 Alkalinizing Agents
- 40:10 Ammonia Detoxicants
- 40:12 Replacement Solutions
- 40:16 Sodium-Removing Resins
- 40:17 Calcium-Removing Resins
- 40:18 Potassium-Removing Resins
- 40:20 Caloric Agents
- 40:24 Salt and Sugar Substitutes
- 40:28 Diuretics
- 40:36 Irrigating Solutions
- 40:40 Uricosuric Agents

44:00 Enzymes

48:00 Antitussive Expectorants, and Mucolytic Agents
- 48:08 Antitussives
- 48:16 Expectorants
- 48:24 Mucolytic Agents

52:00 Eye, Ear, Nose, and Throat (EENT) Preparations
- 52:04 Anti-Infectives
- 52:08 Anti-Inflammatory Agents
- 52:10 Carbonic Anhydrase Inhibitors
- 52:12 Contact Lens Solutions
- 52:16 Local Anesthetics
- 52:20 Miotics
- 52:24 Mydriatics
- 52:28 Mouthwashes and Gargles
- 52:32 Vasoconstrictors
- 52:36 Miscellaneous EENT Drugs

56:00 Gastrointestinal (GI) Drugs
- 56:04 Antacids and Adsorbents
- 56:08 Antidiarrhea Agents
- 56:10 Antiflatulents
- 56:12 Cathartics and Laxatives
- 56:14 Cholelitholytic Agents
- 56:16 Digestants
- 56:20 Emetics
- 56:22 Antiemetics
- 56:24 Lipotropic Agents
- 56:40 Miscellaneous GI Drugs

60:00 Gold Compounds

64:00 Heavy Metal Antagonists

68:00 Hormones and Synthetic Substitutes
- 68:04 Adrenals
- 68:08 Androgens
- 68:12 Contraceptives
- 68:16 Estrogens
- 68:18 Gonadotropins
- 68:20 Antidiabetic Agents
- 68:24 Parathyroid
- 68:28 Pituitary
- 68:32 Progestins
- 68:34 Other Corpus Luteum Hormones
- 68:36 Thyroid and Antithyroid Agents

72:00 Local Anesthetics

76:00 Oxytocics

78:00 Radioactive Agents

80:00 Serums, Toxoids, and Vaccines
    80:04 Serums
    80:08 Toxoids
    80:12 Vaccines

84:00 Skin and Mucous Membrane Agents
    84:04 Anti-Infectives
    84:06 Anti-Inflammatory Agents
    84:08 Antipruritics and Local Anesthetics
    84:12 Astringents
    84:16 Cell Stimulants and Proliferants
    84:20 Detergents
    84:24 Emollients, Demulcents, and Protectants
    84:28 Keratolytic Agents
    84:32 Keratoplastic Agents
    84:36 Miscellaneous Skin and Mucous Membrane Agents
    84:50 Depigmenting and Pigmenting Agents
    84:80 Sunscreen Agents

86:00 Smooth Muscle Relaxants
    86:08 Gastrointestinal Smooth Muscle Relaxants
    86:12 Genitourinary Smooth Muscle Relaxants
    86:16 Respiratory Smooth Muscle Relaxants

88:00 Vitamins
    88:04 Vitamin A
    88:08 Vitamin B Complex
    88:12 Vitamin C
    88:16 Vitamin D
    88:20 Vitamin E
    88:24 Vitamin K Activity
    88:28 Multivitamin Preparations

92:00 Unclassified Therapeutic Agents

94:00 Devices

96:00 Pharmaceutical Aids

AHFS American Hospital Formulary Service Drug Information 85
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ATTACHMENT I

Item 17

DRUG
UTILIZATION
in the
U.S.-1986

Eighth Annual
Review

December 1987

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF EPIDEMIOLOGY AND BIOSTATISTICS

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Drug Utilization in the U.S. - 1986

Eighth Annual Review

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Office of Epidemiology and and Biostatistics
Center for Drugs and Biologics
Food and Drug Administration

This report is the Food and Drug Administration's eighth annual review of prescription drug use in the United States. As in previous years, data are provided on overall drug use and prescriptions for major therapeutic classes, drug categories, and prescription products. The outpatient use of new chemical entities approved by the FDA from 1980 to 1986 is reviewed and "special sections" present an overview of drug use by women and by the elderly. Other special sections describe the use of analeptics, cyclosporine, phenylbutazone, isotretinoin, and antidepressants. A bibliography of selected drug use studies that were published in 1986 is included as an Appendix.

DATA SOURCES

All drug utilization data were derived from three pharmaceutical marketing data bases purchased by FDA from IMS America Ltd.[1] The National Prescription Audit (NPA) is based on a panel of computerized pharmacies, National Disease and Therapeutic Index (NDTI) estimates are derived from information reported by a panel of office-based physicians, and the U.S. Pharmaceutical Market - Drug Store and Hospital Purchases (USD and USH) is a two-part system generated from purchase invoices of drug stores and hospitals. Population estimates are from the U.S. Bureau of the Census. The data bases are described in more detail below.

National Prescription Audit (NPA)

The NPA provides information on prescriptions dispensed by chain and independent pharmacies in the contiguous United States. Other outlets such as discount stores and supermarkets with pharmacies are not included. The NPA data collection methodology was changed in 1981, so changes from 1980-1981 in the number of prescriptions reported may reflect methodological revisions as well as actual changes in drug use. Prior to 1981, data were obtained from a representative sample of 800 pharmacies, each of which was audited for two days per month. Since 1981, IMS has based the NPA national projections on prescriptions dispensed by a panel of 1200 computerized pharmacies. The panel does not represent a true random sample; however, IMS does ensure that the panel is representative of U.S. pharmacies in terms of region, type of ownership, and size.

All data are extrapolated to the national level. IMS revised the extrapolation methodology at the end of 1983, so two sets of NPA data are available for that year. All data in this review are based on the revised methodology.

For each drug, NPA provides estimates of the total number of prescriptions dispensed from retail pharmacies, how many of these were new and how many were refills, and the average number of capsules, tablets, or other units per prescription. All variables except units are also aggregated to provide overall data for drug categories.

National Disease and Therapeutic Index (NDTI)

The NDTI provides descriptive information on disease patterns and treatments in office-based practice in the United States. Data are obtained from a panel of over 2,000 physicians who report case history information on each private patient seen or contacted in any way, regardless of location. The reporting variables include drugs, diagnoses (classified by ICD7), patient age and sex, the location of the visit (in the office, hospital, over the telephone), the type of visit (first, subsequent, or referral), therapy (new vs. continuing), drug issuance (by formal prescription, hospital order, recommendation), how often the patient has been seen, and the time since the last visit. The data are tabulated for each drug product and each major therapeutic category.

Drug reports do not equate exactly to written prescription: only about 61% of the drugs recorded during a physician-patient contact in 1986 involved issuance of a formal prescription (with the remainder representing drugs that were administered directly, given as a sample, or recommended by the physicians and drugs physicians prescribed for patients in hospitals or nursing homes). In addition, refill prescriptions not involving a physician-patient contact are not captured by the NDTI, leading to an underestimation of chronic therapies if drug reports are viewed as prescriptions. By convention the NDTI employs the term "mentions" for such reports: "mentions" reflect usage, but should not be interpreted as directly equivalent to prescriptions or patients. Mentions represent drugs prescribed, recommended, or given in any medical setting by private physicians in office-based practice.

U.S. Pharmaceutical Market - Drug Store and Hospital Purchases (USD and USH)

The USD measures the flow of proprietary and ethical pharmaceuticals from wholesalers and warehouses into drug stores. (Ethical drugs are those that require a written prescription and those that can be purchased without a prescription, or over the counter (OTC), but are promoted only to physicians. Proprietary drugs are those that can be purchased over the counter and are promoted directly to the consumer.) Every month data are collected from the invoices of a panel of 840 drug stores and a near census of wholesalers and warehousing chain operations. Based on these data, the USD provides national estimates of the dollar cost to pharmacies and the number of units purchased for each product/package size. Dollars are aggregated to the product and manufacturer levels. The USH measures purchases by acute care nonfederal hospitals and is the only data base we have that quantifies hospital drug use. However, it only provides information at a very gross level (as does the USD), with no qualitative data on how the drugs are used. Data are collected from a panel of 350 hospitals and a near census of wholesalers. As with the USD, dollar cost and the number of units purchased for each product/package size are extrapolated nationally.

In both the USD and the USH, information on drug quantity is available for individual products only by strength and package size within manfacturer, and totals are not provided at the product or class levels. Cost data (dollars and percentage change) are summarized for individual drugs and classes.

IMS estimates that the USD and the USH combined are representative of 98% of the ethical pharmaceutical market, with the remainder representing direct physician dispensing. This may be an overestimate since distribution of prescription drugs through other sources such as supermarket pharmacies is increasing. However, we believe that the USD and the USH do capture the vast majority of ethical pharmaceutical purchases. The data bases are not as comprehensive for the proprietary or OTC market, but they are our only source of data on OTC drugs. Since major sources of OTC drug purchases such as supermarkets are not measured, as much as one half of all sales for a drug like aspirin may be missing from the USD.

OVERALL DRUG USE

NPA data indicated that 1.56 billion prescriptions were dispensed from retail pharmacies in 1986 (up 0.6% over 1985). The number of new prescriptions accounted for 50% of all prescriptions (with refills accounting for the remaining 50%).

Figure 1 shows trends in overall drug use from 1982 to 1986. The number of prescriptions dispensed from retail pharmacies increased by slightly over 4% during this period; however, the size of the U.S. civilian population increased by just under 4%,[2] with the net effect that the average number of prescriptions per person remained stable at 6.5 prescriptions. Data were not adjusted for changes in prescription size as the 1986 prescription size index was not available when this review was written. However, average prescription size increased by less than 1% from 1982 to 1985.

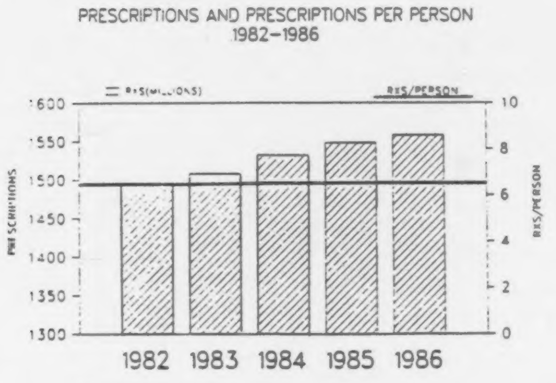

Figure 1

MAJOR THERAPEUTIC CLASSES AND DRUG CATEGORIES

The IMS data bases combine individual drugs into therapeutic groups by the Uniform System of Classification (USC), which is a hierarchical system. At the broadest level of categorization, 16 major therapeutic classes each accounted for at least 2% of all prescriptions dispensed from retail pharmacies in 1986. As a group, these classes represented 86% of total prescriptions. As indicated in Table 1, cardiovascular drugs, with 15% of the prescription market, were the most frequently dispensed followed by systemic antiinfectives (13%) and psychotherapeutic drugs (8%). These classes along with analgesics and diuretics accounted for around half of all 1986 prescriptions.

Table 1 also provides data for more specific drug categories within the broader therapeutic classes. Only those categories representing at least 2% of the total market are included. For example, systemic antiarthritics represented about 4% of all prescriptions and accounted for 66 million of the 76 million antiarthritic prescriptions dispensed in 1986. The remaining 10 million prescriptions were dispensed for topical and gout-specific antiarthritics, but neither of these categories represented at least 2% of the market.

The only change from 1985 to 1986 in the major therapeutic class rankings was a switch in the positions of contraceptives and bronchial therapy, with bronchial drugs moving from the eleventh to the tenth position. Among the specific drug categories, fungicides (the most commonly dispensed dermatologicals) appeared for the first time in 1986, while tetracyclines and propoxyphene analgesics were dropped from the rankings. Thiazides and "other" diuretics switched positions, with thiazides becoming the least frequently dispensed category of oral diuretics.

Table 1. Major Therapeutic Classes and Drug Categories Representing at Least 2% of Total 1986 Rxs

Rank	Class/Category	Rxs in Millions	% Total Rxs	% Change 1985-1986
1	Cardiovascular drugs	239	15	4
	Beta/alpha-beta blockers	63	4	1
	Antihypertensives	58	4	5
	Vasodilators	54	3	0
	Digitalis	27	2	1
2	Systemic antiinfectives	201	13	3
	Amoxicillin	42	3	18
	Erythromycin	34	2	2
	Cephalosporins	28	2	13
	Penicillin (G and V/VK)	26	2	-1
3	Psychotherapeutic drugs	132	8	-1
	Benzodiazepine tranquilizers	61	4	0
	Antidepressants	33	2	3
4	Ethical analgesics	112	7	-3
	Codeine	60	4	-4
5	Diuretics	104	7	-3
	Potassium-sparing	44	3	0
	"Other"(eg. furosemide)	31	2	1
	Thiazides	29	2	-12
6	Hormones	87	6	0
	Plain corticoids	47	3	-1
	Sex hormones	28	2	5
7	Antiarthritics	76	5	0
	Systemic antiarthritics	66	4	1
8	Antispasmodics and GI/GU	54	3	1
	"Other" antispasmodics (eg. cimetidine, sucralfate)	32	2	8
9	Cough and cold preparations	54	3	-2
	Oral cold preparations, Rx	25	2	-8
10	Bronchial therapy	52	3	5
	Xanthines/combos	25	2	0
11	Contraceptives	52	3	2
	Oral contraceptives	51	3	2
12	Dermatologicals	39	3	2
	Fungicides	24	2	2
13	Ophthalmic preparations	38	2	2
14	Nutrients and supplements	37	2	0
	Potassium supplements	33	2	0
15	Diabetes therapy	36	2	6
16	Ethical sedatives	30	2	-1
	Total 16 classes	1343	86	

Source: National Prescription Audit.

PRESCRIPTION PRODUCTS

Table 2 lists the 25 prescription drug products most frequently dispensed from retail pharmacies in 1986. Only three of these products - Procardia, Halcion, and Ceclor - were not among the 25 leading products in 1985. They replaced Aldomet (# 28 in 1986), Ativan (# 30 in 1986) and Feldene (# 29 in 1986) on the top 25 list. Valium and Inderal, drugs for which generic versions became available in 1985, showed the greatest decreases in number of prescriptions from 1985 to 1986 (see Table 2). If we consider total prescriptions for the drug entities, prescription volume decreased by 10% for both propranolol and diazepam (as compared to -37% for Inderal and -38% for Valium). Generic ibuprofen also became available in 1985, but prescription volume for Motrin did not change from 1985 to 1986. The greatest increases in dispensed prescriptions were seen for Zantac (+34%), Xanax (+29%), and Halcion (+29%).

Table 2. Leading Prescription Products in 1986

Product	Rank in 1986	Rank in 1985	% Change Rxs 1985-1986
Dyazide	1	1	-6
Lanoxin	2	2	0
Amoxil	3	6	7
Tylenol w/Codeine	4	5	-14
Tagamet	5	7	-7
Xanax	6	15	29
Inderal	7	3	-37
Lasix	8	8	-15
Motrin	9	10	0
Tenormin	10	13	15
Valium	11	4	-38
Keflex	12	11	3
Naprosyn	13	14	3
Darvocet-N 100	14	9	-25
Premarin	15	12	-3
Zantac	16	25	34
Synthroid	17	16	4
Lopressor	18	17	-1
Theo-Dur	19	18	-1
Procardia	20	26	13
Slow-K	21	20	-5
Dilantin Sodium	22	22	-2
Halcion	23	32	29
Ceclor	24	34	26
E.E.S.	25	23	-8

NEW CHEMICAL ENTITIES

Twenty new chemical entities (NCEs) and five new biological products were approved for marketing in the U.S. in 1986. These are listed in Table 3 along with the date of FDA approval and the initial marketing date (as determined by using USD and USH to identify the month in which each product first appeared or as indicated by the manufacturer for those products not picked up by the IMS data bases).

Table 3. New Chemical Entities Approved in 1986

Generic Name	Brand Name	Approval Date-FDA	Marketing Date-IMS	Drug Type
Alfentanil HCl	Alfenta	12/29/86	-	Anesthetic
Aztreonam	Azactam	12/31/86	2/87	Antibiotic
Buspirone HCl	Buspar	9/29/86	9/86	Tranquilizer
Calcitonin, human	Cibacalcin	10/31/86	12/86	Synthetic hormone for Paget's disease
Clofazimine	Lamprene	12/15/86	-	For leprosy
Encainide HCl	Enkaid	12/21/86	4/87	Antiarrhythmic
Esmolol HCl	Brevibloc	12/31/86	-	Beta-blocker, antiarrhythmic
Etretinate	Tegison	9/30/86	11/86	For severe psoriasis
Famotidine	Pepcid	10/15/86	11/86	H_2 receptor antagonist, antiulcer
Flurbiprofen	Ocufen	12/31/86	5/87	Inhibition of intraoperative miosis
Guanfacine HCl	Tenex	10/27/86	1/87	Antihypertensive
Ipratropium Br	Atrovent	12/29/86	3/87	Bronchodilator
Ketoprofen	Orudis	1/09/86	1/86	Antiarthritic
Methacholine Cl	Provocholine	10/31/86	-	Diagnostic agent for asthma
Norfloxacin	Noroxin	10/31/86	11/86	Antibiotic
Permethrin	Nix	3/31/86	6/86	Pediculocide
Pirbuterol acetate	Exirel	12/30/86	-	Bronchodilator
Sulbactam Na/ ampicillin Na	Unasyn	12/31/86	-	Antibiotic
Technetium, Tc-99M, lidofenin kit	Technescan HIDA Kit	10/31/86	-	Radioactive diagnostic
Tranexamic acid	Cyklokapron	12/30/86	-	Hemostatic agent
Biologics:				
Digoxin immune FAB, ovine	Digibind	4/22/86	-	For digitalis intoxication
Hepatitis B vaccine, recombinant	Recombivax HB	7/23/86	2/87	Hepatitis vaccine
Interferon alpha	Roferon-A, Intron-A	6/04/86	6/86	For hairy cell leukemia
Muromonab-CD3	Orthoclone OKT3	6/19/86	7/86	For renal transplants (acute rejection)
Porcine antihemophilic factor VIII:C	Hyate:C	10/08/86	-	Hemostatic

FDA approved 153 NCEs and seven new biological products from 1980 to 1986. For 62 of these, at least 100,000 prescriptions have been dispensed since the drug was first marketed. These 62 NCEs are listed in Table 4 along with their year of initial marketing, prescription volume in 1986, percentage of total 1986 prescriptions for the major therapeutic class under which they are categorized by IMS, and cumulative prescriptions from initial marketing through 1986. The table ranks therapeutic classes by cumulative number of prescriptions.

As a class, cardiovascular NCEs have experienced the greatest success in the marketplace. Over 150 million prescriptions were dispensed between 1980 and 1986 for the 14 cardiovascular drugs listed in Table 4. These 14 NCEs accounted for about one-quarter of total 1986 prescriptions for cardiovascular drugs.

The three individual drugs with the greatest number of cumulative prescriptions were atenolol (49 million prescriptions), albuterol (44 million prescriptions), and alprazolam (40 million prescriptions). All three were marketed in 1981 and so their cumulative totals represent six years of prescriptions (more than the majority of the NCEs listed). These three drugs also had the greatest number of 1986 prescriptions.

Two NCEs represented 100% of their therapeutic class: nicotine resin complex (smoking deterrents) and acyclovir (antivirals). Temazepam and triazolam accounted for almost one-half of all 1986 prescriptions for sedative hypnotics, and the three diabetes NCEs approved in 1983 and 1984 represented about one-third of 1986 prescriptions for diabetes therapy. (NB: Over-the-counter purchases of insulin are not reflected in the latter estimate.)

Table 4. New Chemical Entities (NCEs) Approved 1980-1986
for Which at Least 100,000 Rxs Have Been Dispensed (N=62)

Class/Generic Name	Brand Name(s)	Year Mkted	Thousand Rxs 1986	% Total Class 1986	Million Rxs 1980-1986
Cardiovascular drugs (14 NCEs)			58460	24.5	151.7
Acebutolol HCl	Sectral	1985	518	0.2	0.6
Atenolol	Tenormin,Tenoretic	1981	15319	6.4	48.7
Captopril	Capoten,Capozide	1981	8545	3.6	20.0
Diltiazem	Cardizem	1982	8360	3.5	11.6
Enalapril maleate	Vasotec,Vasoretic	1986	2546	1.1	2.5
Flecainide acetate	Tambocor	1986	234	0.1	0.2
Guanabenz acetate	Wytensin	1981	1276	0.5	4.3
Guanadrel SO_4	Hylorel	1983	249	0.1	0.7
Labetolol HCl	Normodyne,Trandate	1984	2477	1.0	4.1
Nifedipine	Procardia	1982	9709	4.1	35.3
Pentoxifylline	Trental	1984	2567	1.1	4.4
Pindolol	Visken	1982	1497	0.6	4.5
Tocainide HCl	Tonocard	1984	762	0.3	1.2
Verapamil	Isoptin, Calan	1982	4403	1.8	13.6
Psychotherapeutic drugs (6 NCEs)			20430	15.5	69.2
Alprazolam	Xanax	1981	14728	11.2	40.1
Amoxapine	Asendin	1980	926	0.7	6.5
Halazepam	Paxipam	1981	86	0.1	0.9
Maprotiline	Ludiomil	1981	1091	0.8	8.6
Nomifensine maleate	Merital	1985	47	<0.1	0.2
Trazodone	Desyrel	1982	3599	2.7	12.9
Antiarthritics (5 NCEs)			10767	14.3	50.8
Auranofin	Ridaura	1985	298	0.4	0.4
Benoxaprofen	Oraflex	1982	0	0.0	0.8
Ketoprofen	Orudis	1986	896	1.2	0.9
Meclofenamate Na	Meclomen	1980	1894	2.5	12.3
Piroxicam	Feldene	1982	7679	10.2	36.4
Sedatives (2 NCEs)			14301	47.3	46.9
Temazepam	Restoril	1981	5436	18.0	24.6
Triazolam	Halcion	1983	8865	29.3	22.3
Bronchial therapy (2 NCEs)			12738	24.4	44.6
Albuterol	Proventil,Ventolin	1981	12528	24.0	44.3
Bitolterol mesylate	Tornalate	1985	210	0.4	0.3
Antispasmodics and GI/GU (2 NCEs)			14027	26.1	35.0
Ranitidine	Zantac	1983	11403	21.2	27.4
Sucralfate	Carafate	1981	2624	4.9	7.6
Analgesics (3 NCEs)			3355	3.0	26.9
Diflunisal	Dolobid	1982	2712	2.4	11.6
Zomepirac	Zomax	1980	0	0.0	14.7
Suprofen	Suprol	1986	643	0.6	0.6
Diuretics (3 NCEs)			7794	7.5	25.9
Amiloride	Midamor,Moduretic	1981	4620	4.4	18.1
Bumetanide	Bumex	1983	1817	1.7	4.7
Indapamide	Lozol	1983	1357	1.3	3.1
Diabetes therapy (3 NCEs)			12267	34.3	21.7
Biosynthetic human insulin	Humulin	1983	3358	9.4	6.4
Glipizide	Glucotrol	1984	2668	7.5	4.6
Glyburide	Micronase,Dia Beta	1984	6241	17.5	10.7

Table 4 (Continued). New Chemical Entities (NCEs) Approved 1980-1986
for Which at Least 100,000 Rxs Have Been Dispensed (N=62)

Class/Generic Name	Brand Name(s)	Year Mkted	Thousand Rxs 1986	% Total Class 1986	Million Rxs 1980-1986
Systemic antiinfectives (3 NCEs)			4520	2.2	12.1
Amoxicillin/ K Clavulanate	Augmentin	1984	3980	2.0	7.1
Bacampicillin HCl	Spectrobid	1981	259	0.1	3.8
Cinoxacin	Cinobac	1981	281	0.1	1.4
Dermatologicals (8 NCEs)			3272	8.3	11.4
Ciclopirox olamine	Loprox	1983	759	1.9	2.4
Econazole NO_3	Spectazole	1983	334	0.8	1.0
Isotretinoin	Accutane	1982	802	2.0	3.0
Ketoconazole	Nizoral	1981	794	2.0	3.7
Meclocycline sulfosalicylate	Meclan	1980	91	0.2	0.8
Butaconazole NO_3	Femstat	1986	492	1.3	0.5
Systemic antihistamines (1 NCE)			6812	35.8	9.3
Terfenadine	Seldane	1985	6812	35.8	9.3
Smoking Deterrents (1 NCE)			2921	100.0	8.7
Nicotine resin complex	Nicorette	1984	2921	100.0	8.7
Antivirals (1 NCE)			2530	100.0	6.9
Acyclovir	Zovirax	1982	2530	100.0	6.9
Hormones (2 NCEs)			2111	2.4	6.7
Flunisolide	Nasalide,Aerobid	1981	1862	2.1	6.5
Clobetasol	Temovate	1986	249	0.3	0.2
Cholestrol reducers/lipotropics (1 NCE)			1817	42.7	4.2
Gemfibrozil	Lopid	1982	1817	42.7	4.2
Ophthalmic preparations (3 NCEs)			1802	4.7	2.4
Betaxolol HCl	Betoptic	1985	1350	3.5	1.5
Trifluridine	Viroptic	1980	104	0.3	0.6
Levobunolol HCl	Betagan	1986	348	0.9	0.3
Muscle relaxants (1 NCE)			95	0.5	0.5
Ritodrine HCl	Yutopar	1980	95	0.5	0.5
Antimalarials (1 NCE)			39	2.2	0.2
Sulfadoxine/ pyrimethamine	Fansidar	1982	39	2.2	0.2
Pediculocides/scabicides (1 NCE)			118	4.9	0.1
Permethrin	Nix	1986	118	4.9	0.1
Cancer therapy (1 NCE)			93	2.3	0.1
Cyclosporine	Sandimmune	1983	93	2.3	0.1

Source: National Prescription Audit.

Table 4 includes those NCEs that were used relatively frequently on an outpatient basis. The fact that a NCE did not appear on this table does not necessarily mean that it is an infrequently used drug. As shown in Table 5, many of the other NCEs are drugs that would be used primarily or exclusively in a hospital setting. Not many outpatient prescriptions are dispensed for injectable cephalosporins, and none at all are dispensed for radioactive diagnostic agents. Many of the NCEs listed in Table 5 had not yet been marketed by the end of 1986 or had not been on the market long enough to reach the criterion for inclusion in Table 4.

On both Tables 4 and 5, NCEs are grouped by therapeutic class as assigned under the Uniform System of Classification (USC). USC categorization may not always correspond with therapeutic indication. For example, midazolam, an injectable benzodiazepine, was approved in 1985 as a general anesthetic but is grouped by USC with benzodiazepine tranquilizers as a psychotherapeutic drug. Similarly, cyclosporine is grouped with other immunosuppressives under cancer therapy although it is used to suppress rejection of transplanted organs.

Table 5. New Chemical Entities (NCEs) and Biological Products Approved 1980-1986 for Which Less Than 100,000 Rxs Have Been Dispensed (N=98)

Class/Generic Name	Brand Name(s)	Year Approved
Systemic antiinfectives (22 NCEs)		
Amdinocillin	Coactin	1984
Azlocillin Na	Azlin	1982
Aztreonam	Azactam	1986
Cefonocid Na	Monocid	1984
Cefoperazone Na	Cefobid	1982
Ceforanide	Precef	1984
Cefotaxime Na	Claforan	1981
Cefotetan disodium	Cefotan	1985
Ceftazidime	Fortaz	1985
Ceftizoxime Na	Cefizox	1983
Ceftriaxone Na	Rocephin	1984
Cefuroxime Na	Zinacef	1983
Imipenem/cilastatin Na	Premaxin	1985
Mezlocillin	Mezlin	1981
Moxalactam disodium	Moxam	1981
Netilmicin SO_4	Netromycin	1983
Norfloxacin	Noroxin	1986
Pentamidine isethionate	Pentam 300	1984
Piperacillin Na	Pipracil	1981
Praziquantel	Biltricide	1982
Sisomicin SO_4	Siseptin	1980
Sulbactam Na/Ampicillin Na	Unasyn	1986
Diagnostic aids (16 NCEs)		
Bentiromide	Chymex	1983
Ceruletide	Tymtran	1981
Indium In-III oxyquinolone	-	1985
Iodohippurate Na, I-123	Nephroflow	1984
Iohexal	Omnipaque	1985
Iopamidol	Isovue	1985
Ioxoglate meglimine/ioxoglate Na	Hexabrix	1985
Isosulfan blue	Lymphazurin	1981
Methacholine Cl	Provocholine	1986
Penetate indium disodium In 111	MPI Indium DTPA In 111	1982
Saralasin acetate	Sarenin	1981
Secretin	Secretin Kabi	1981
TC 99M - disofenin	Hepatolite	1982
TC 99M - lidofenin	Technescan Kit	1986
TC 99M - succimer	MPI DMSA Kidney Reagent	1982
Xenon Xe 127	-	1982
Cardiovascular drugs (9 NCEs)		
Alprostadil	Prostin VR Ped	1981
Amiodarone HCl	Cordarone	1985
Amrinone	Inocor	1984
Bethanidine SO_4	Tenathan	1981
Encainide HCl	Enkaid	1986
Esmolol HCl	Brevibloc	1986
Guanfacine HCl	Tenex	1986
Mexiletine HCl	Mexitil	1985
Oxprenolol HCl	Trasicor	1983
Miscellaneous ethical drugs (9 NCEs)		
Acetohydroxamic acid	Lithostat	1983
Clofazamine	Lamprene	1980
Gonadorelin HCl	Factrel	1982
Malathion	Prioderm	1982
Monooctanoin	Moctanin	1985
Na cellulose PO_4	Calcibind	1982
Naltrexone HCl	Trexan	1984
Trientine HCl	Cuprid	1985
Trilostane	Modrastane	1984
Biologicals (7 NCEs)		
Digoxin immune FAB	Digibind	1986
Haemophilus B polysaccaride vaccine	b-Capsa 1, HibVax, Hib-Imune	1985
Hepatitis B vaccine	Heptavax B	1982
Hepatitis B vaccine (recombitant)	Recombivax HB	1986
Interferon alpha	Roferon-A, Intron-A	1986
Muromonab-CD3	Orthoclone OKT3	1986
Porcine antihemophilic factor VIII:C	Hyate:C	1986

Table 5 (Continued). New Chemical Entities (NCEs) and Biological Products Approved 1980-1986 for Which Less Than 100,000 Rxs Have Been Dispensed (N=98)

Class/Generic Name	Brand Name(s)	Year Approved
Cancer therapy (4 NCEs)		
Estramustine PO_4	Emcyt	1981
Etoposide	Vepesid	1983
Leuprolide acetate	Lupron	1985
Streptozocin	Zanosar	1982
Dermatologicals (4 NCEs)		
Aclometasone dipropionate	Vaderm	1982
Etretinate	Tegison	1986
Sulconazole NO_3	Sulcosyn	1985
Ticonazole	Trosyd	1983
Psychotherapeutic drugs (4 NCEs)		
Buproprion HCl	Wellbutrin	1985
Buspirone HCl	Busper	1986
Midazolam HCl	Versed	1985
Pimozide	Orap	1984
Anesthetics (3 NCEs)		
Alfentanil HCl	Alfenta	1986
Etomidate	Amidate	1982
Sufentanil	Sufenta	1984
Hormones (3 NCEs)		
Calcifediol	Calderol	1980
Human calcitonin	Cibacalcin	1986
Somatrem	Protropin	1985
Anthelmintics (2 NCEs)		
Niclosamide	Niclocide	1982
Oxamniquine	Vansil	1980
Antinauseants (2 NCEs)		
Dronabinol	Marinol	1985
Nabilone	Cesamet	1985
Bronchial therapy (2 NCEs)		
Ipratropium Br	Atrovent	1986
Pirbuterol acetate	Exirel	1986
Muscle relaxants (2 NCEs)		
Atracurium besylate	Tracrium	1983
Vecuronium Br	Norcuron	1984
Analgesics (1 NCE)		
Buprenorphine	Buprenex	1981
Antispasmodics & GI/GU (1 NCE)		
Famotidine	Pepcid	1986
Antivirals (1 NCE)		
Ribavirin	Virazole	1985
Bile therapy (1 NCE)		
Chenodiol	Chenix	1983
Enzymes (1 NCE)		
Chymopapain	Chymodiactin, Discase	1982
Hemostatics (1 NCE)		
Tranexamic acid	Cyclokapron	1986
Nutrients and Supplements (1 NCE)		
L-carnitine	Vitacarn, Carnicor	1985
Ophthalmic preparations (1 NCE)		
Flurbiprofen	Ocufen	1986
Sedatives (1 NCE)		
Quazepam	Dormalin	1985

PRESCRIBING OF DRUGS FOR THE ELDERLY

In 1986, the elderly (people 65 years and older) made up 12% of the U.S. resident population. That same year, according to the NDTI, they accounted for 25% of all visits to physicians and 32% of all drug mentions. This latter percentage has been gradually increasing. Figure 2 shows trends in total drug mentions and the percent of these mentions that were for the elderly from 1974 through 1986. The elderly represented only 24% of all drug mentions in 1974. The actual number of all mentions regardless of age decreased from 1974 through 1980 and has increased since then.

TOTAL DRUG MENTIONS AND PERCENT OF MENTIONS
FOR AGE 65+ YEARS OLD

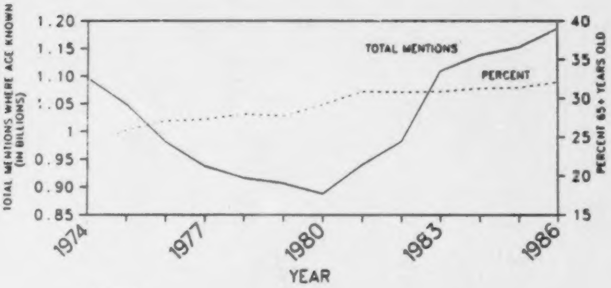

Figure 2

Not surprisingly, the elderly differ from people less than 65 years old in the type of drugs used and the rate of such use. Table 6 provides a listing of the major classes and the specific categories of drugs accounting for at least 2% of all drug mentions in both the elderly and those people younger than 65 years. The table also contains an estimate of the magnitude of exposure as measured by the number of mentions per 100 population.

At an aggregate level, the elderly accounted for 1304 drug mentions per 100 population compared to only 380 mentions per 100 population in people less than 65 years old. The cardiovascular agents were the most frequently used class of drugs in the elderly, accounting for 25% of all mentions. In 1986 these drugs were used at a rate of 327 mentions per 100 population in the elderly compared to 31 mentions per 100 population in younger people. The cardiovascular class ranked third in people less than 65 years and accounted for 8% of all drug mentions.

The antiinfectives were the most frequently used class of drugs in people less than 65 years old, with almost 20% of all drug mentions. Four separate categories (amoxicillin, erythromycin, the cephalosporins and the penicillins) each accounted for more than 2% of all drug mentions for this age group. Conversely, in the elderly the antiinfectives ranked third with only 9% of all mentions. The cephalosporin category was the only specific group of antiinfectives that comprised more than 2% of all mentions. Although antiinfectives ranked third in the elderly compared to first in the younger group, the rate of use was higher in the elderly with 117 mentions per 100 population compared to 74 mentions per 100 population in people less than 65 years old.

All of the top four classes in the elderly (cardiovascular agents, diuretics, antiinfectives, and analgesics) were used at a higher rate than the most frequently used class in the younger group (antiinfectives). These four classes accounted for over half of all drug mentions for the elderly.

The only class with more than 2% of drug mentions in the elderly that did not attain at least 2% of drug mentions in the younger group was the nutrients/supplements class (mainly potassium). Cough/cold products, dermatologicals, vitamins, and biologicals all accounted for at least 2% of drugs used in the younger group while they did not do so in the elderly.

Table 6. Prescribing of Drugs in 1986 by Age
Major Classes and Specific Categories Accounting for at Least 2% of All Drug Mentions

65+ Years Old					Less than 65 Years Old				
Rank	Class/Category	#Mentions (in Thousands)	% of Total Mentions	#Mentions/100 Population*	Rank	Class/Category	#Mentions (in Thousands)	% of Total Mentions	#Mentions/100 Population*
1	Cardiovascular agents	95273	25.0	327	1	Antiinfectives	157706	19.6	74
	Antihypertensives	20306	5.3	70		Amoxicillin	36381	4.5	17
	Coronary vasodilators	20448	5.4	70		Erythromycin	25067	3.1	12
	Digitalis preparations	19836	5.2	68		Cephalosporins	22955	2.8	11
	Alpha/beta blockers	16969	4.5	58		Penicillins	18441	2.3	9
	Calcium blockers	9864	2.6	34					
2	Diuretics	40788	10.7	140	2	Analgesics	68889	8.6	32
						Nonnarcotics	29995	3.7	14
						Narcotics	38894	4.8	18
						(codeine-containing)	(23065)	(2.9)	(11)
3	Antiinfectives	34252	9.0	117	3	Cardiovascular agents	65409	8.1	31
	Cephalosporins	9881	2.6	34		Alpha/beta blockers	22653	2.8	11
4	Analgesics	25090	6.6	86	4	Cough/cold products	54908	6.8	26
	Nonnarcotics	11135	2.9	38					
	(aspirin)	(7426)	(2.0)	(25)					
	Narcotics	13955	3.7	48					
5	Diabetes therapy	17971	4.7	62	5	Psychotherapeutic agents	54892	6.8	26
	Insulin	8993	2.4	31		Minor tranquilizers	23284	2.9	11
	Oral hypoglycemics	8978	2.4	31		Antidepressants/lithium	20562	2.6	10
6	Psychotherapeutics	17159	4.5	59					
7	Ophthalmics	16811	4.4	58	6	Antiarthritics	33237	4.1	16
	Miotics/glaucoma	8113	2.1	28	7	Corticoids, plain	30784	3.8	14
8	Antiarthritics	16744	4.4	57	8	Dermatologicals	30799	3.8	14
9	Corticoids, plain	12439	3.3	43	9	Diuretics	27374	3.4	13
10	Bronchial therapy	12328	3.2	42	10	Vitamins	22401	2.8	11
	Bronchodilators	12157	3.2	42					
11	Antispasmodics GI/GU	11242	3.0	39	11	Bronchial therapy	21358	2.7	10
						Bronchodilators	20337	2.5	10
12	Nutrients/supplements	9780	2.6	34	12	Antispasmodics GI/GU	19388	2.4	10
	Potassium	7796	2.0	27	13	Diabetes therapy	18602	2.3	9
					14	Biologicals	18009	2.2	8
					15	Ophthalmics	17129	2.1	8
	Total all classes	380,290	100	1304		Total all classes	805,584	100	380

Source: National Disease and Therapeutic Index.

* U.S. resident population as of July 1, 1986: less than 65 yrs. = 211,908,000; 65+ yrs. = 29,173,000.

Switching to specific drugs used in the elderly in 1986, Table 7 lists the top 25 drugs as specified by the prescribing physician. It is important to note that the drugs are listed as written - i.e., Lanoxin^R and digoxin both appear on the list because that is how they were reported by the prescribing physician. Lasix, a diuretic, was the most frequently mentioned. Given that cardiovascular agents and diuretics are the two classes used most frequently by the elderly, it is not surprising that 16 of the 25 drugs belong in one or the other class.

Table 7. Prescribing of Drugs in 1986 for the Elderly (65 Years and Older)
Top 25 Drugs as Specified by the Prescribing Physician

Rank	Drug Name
1	Lasix
2	Lanoxin
3	Dyazide
4	digoxin
5	hydrochlorothiazide
6	Inderal
7	aspirin
8	Persantine
9	Theo-dur
10	nitroglycerin
11	insulin nph
12	Coumadin
13	prednisone
14	Aldomet
15	Procardia
16	Isordil
17	Motrin
18	Tylenol with codeine
19	Tagamet
20	Cardizem
21	Capoten
22	Tenormin
23	Lopressor
24	Timoptic
25	Zantac

Source: National Disease and Therapeutic Index.

PRESCRIBING OF DRUGS BY PATIENT SEX

In 1986, women made up 51% of the U.S. resident population. According to the NDTI, that same year they accounted for 60% of all visits to physicians and a similar percentage of all drug mentions. At an aggregate level, the rate of drug mentions per 100 population was 558 for women compared to 383 for men.

Table 8 provides information by sex on the major classes and the specific categories of drugs accounting for at least 2% of all drug mentions. The rankings are very similar for males and females, although the rate of mentions per 100 population by class or category was generally higher in women than in men. For each sex, 12 major classes individually accounted for at least 2% of all drug mentions. The only differences between the two lists are vitamins, which ranked ninth in women and did not make the 2% cut-off in men, and biologicals, which ranked twelfth in males and did not have at least 2% of mentions in women. However, the rate of drug mentions per 100 population for biologicals was identical in men and women with 8 drug mentions/100 population. The only classes for which the rate of drug mentions/100 population was higher in men was coronary vasodilators (13 in men vs. 11 in women) and bronchial therapy (14 vs. 13).

Table 8. Prescribing of Drugs in 1986 by Sex
Major Classes and Specific Categories Accounting for at Least 2% of All Drug Mentions

Male					Female				
Rank	Class/Category	#Mentions (in Thousands)	% of Total Mentions	#Mentions/ 100 Population*	Rank	Class/Category	#Mentions (in Thousands)	% of Total Mentions	#Mentions/ 100 Population*
1	Antiinfectives	79903	17.8	68	1	Antiinfectives	104476	15.1	84
	Amoxicillin	16878	3.8	14		Amoxicillin	20042	2.9	16
	Cephalosporins	14403	3.2	12		Cephalosporins	17012	2.5	14
	Erythromycin	11375	2.5	10		Erythromycin	16098	2.3	13
2	Cardiovascular agents	71677	15.9	61	2	Cardiovascular agents	81901	11.9	66
	Alpha/beta blockers	16757	3.7	14		Alpha/beta blockers	21048	3.1	17
	Coronary vasodilators	15689	3.5	13		Antihypertensives	20287	2.9	16
	Antihypertensives	14236	3.2	12		Coronary vasodilators	13821	2.0	11
	Digitalis preparations	10622	2.4	9		Digitalis preparations	13363	1.9	11
3	Analgesics	36740	8.2	31	3	Analgesics	53696	7.8	43
	Narcotics	20885	4.6	18		Narcotics	30176	4.4	24
	Nonnarcotics	15855	3.5	14		Nonnarcotics	23510	3.4	19
4	Psychotherapeutic agents	24588	5.5	21	4	Psychotherapeutic agents	44797	6.5	36
	Minor tranquilizers	10264	2.3	9		Minor tranquilizers	19705	2.9	16
	Antidepressants/lithium	8739	1.9	7		Antidepressants/lithium	16123	2.3	13
5	Diuretics	24537	5.4	21	5	Diuretics	40746	5.9	33
	Diuretics, other	9268	2.1	8		K-sparing	14559	2.1	12
	K-sparing	8362	1.9	7		Diuretics, other	13533	2.0	11
6	Cough/cold products	23794	5.3	20	6	Cough/cold products	34738	5.0	28
7	Corticoids	19903	4.4	17	7	Antiarthritics	28376	4.1	23
8	Antiarthritics	19503	4.3	17	8	Corticoids	27794	4.0	22
9	Bronchial therapy	16226	3.6	14	9	Vitamins	21657	3.1	18
	Bronchodilators	15751	3.5	13		Prenatal vitamins	15161	2.2	12
10	Diabetes therapy	13821	3.1	12	10	Diabetes therapy	21006	3.0	17
11	Antispasmodics GI/GU	11637	2.6	10	11	Antispasmodics GI/GU	17675	2.6	14
12	Biologicals	9277	2.1	8	12	Bronchial therapy	15995	2.3	13
						Bronchodilators	15377	2.2	12
Total all classes		449,849	100	383	Total all classes		689,786	100	558

Source: National Disease and Therapeutic Index.

* U.S. resident population as of July 1, 1986: Male = 117,362,000 Female = 123,719,000.

Table 9 lists the top 25 drugs mentioned by prescribing physicians for male and female patients. Again, the rankings are very similar with the exceptions indicated.

Table 9. Prescribing of Drugs in 1986 by Sex
Top 25 Drugs as Specified by the Prescribing Physician

	Drug Name	
Rank	Male	Female
1	amoxicillin	amoxicillin
2	Lasix	Lasix
3	Tylenol with codeine	Lanoxin
4	Lanoxin	Tylenol with codeine
5	Amoxil	Dyazide
6	aspirin	Motrin
7	Dyazide	Amoxil
8	Motrin	ampicillin
9	Keflex	hydrochlorothiazide
10	ampicillin	Inderal
11	Tylenol	prednisone
12	digoxin*	Naprosyn
13	Persantine*	Premarin*
14	Theo-dur	Keflex
15	prednisone	Stuartnatal 1 + 1*
16	Inderal	aspirin
17	hydrochlorothiazide	Tylenol
18	Tenormin*	insulin nph*
19	Naprosyn	Xanax*
20	Tagamet*	Demerol
21	tetracycline	tetracycline
22	nitroglycerin*	EES
23	Ceclor*	Synthroid*
24	EES	Theo-dur
25	Demerol	Darvocet N 100*

Source: National Disease and Therapeutic Index.

* In the top 25 for this sex only.

Prescribing of drugs for women 20-39 years old

Tables 10 and 11 provide data on prescribing of drugs for women of childbearing age. For convenience, this age is defined as 20-39 years old. These data do not indicate whether the women were actually pregnant or at risk of becoming so. The data should only be taken as an aggregate reflection of the national use of drugs in women of this age group.

In 1986, there were approximately 172 million drug mentions for women 20-39 years old (15% of all drug mentions that year), providing a rate of 419 drug mentions per 100 population for these women during the year.

Table 10 displays those major classes and specific categories of drugs that accounted for at least 2% of all drug mentions for the group. Antiinfectives ranked first with 17% of all mentions (a rate of 72 drug mentions per 100 population). Three specific antiinfective categories were over the 2% cut-off: the cephalosporins, erythromycin and amoxicillin. The analgesic class ranked second with almost 10% of all drug mentions (a rate of 41 drug mentions per 100 population). Codeine-containing products comprised 58% of the narcotic analgesic category. As would be expected, vitamins and oral contraceptives rank high in this group of women (#3 and #5 respectively).

Oral contraceptives, fungicides (most of which are vaginal preparations) and hematinics are the only classes of drugs that account for at least 2% of drug mentions in this age group of women and not for women overall.

Table 10. Prescribing of Drugs in 1986 for Women 20-39 Years Old
Major Classes and Specific Categories Accounting for
at Least 2% of all Drug Mentions

Rank	Class/Category	#Mentions (in Thousands)	% of Total	#Mentions/ 100 Population*
1	Antiinfectives	29426	17.1	72
	Erythromycin	5147	3.0	13
	Cephalosporins	4131	2.4	10
	Amoxicillin	3770	2.2	9
2	Analgesics	16702	9.7	41
	Narcotics	10363	6.0	25
	Nonnarcotics	6339	3.7	15
3	Vitamins	14867	8.6	36
	Prenatal vitamins	13481	7.8	33
4	Psychotherapeutic Agents	13767	8.0	34
	Minor tranquilizers	5723	3.3	14
	Antidepressants/lithium	5298	3.1	13
5	Oral contraceptives	10823	6.3	26
6	Cough/cold products	10619	6.2	26
7	Corticoids	7138	4.1	17
8	Antiarthritics	6370	3.7	16
9	Fungicides	5780	3.4	14
	Fungicides, vaginal	4757	2.8	12
10	Antispasmodics GI/GU	3798	2.2	9
11	Hematinics	3583	2.1	9
12	Cardiovascular agents	3415	2.0	8
Total all classes		172113	100	419

Source: National Disease and Therapeutic Index.

*U.S. resident population: women 20-39 years old as of July 1, 1986=41,043,000.

Table 11 lists the top 25 drugs mentioned by prescribing physicians for women 20 - 39 years old. These drugs range from 0.6% to 2.7% of total drug mentions for this group. Within the top 25 drugs, ten are antiinfectives, five are analgesics or antiarthritics, three are prenatal vitamins, three are oral contraceptives, and two are benzodiazepine tranquilizers. The remaining two are a vaginal fungicide and a corticosteroid.

Table 11. Prescribing of Drugs in 1986 for Women 20-39 Years Old
Top 25 Drug Names as Specified by the Prescribing Physician

Rank	Drug Name
1	Stuartnatal 1 + 1
2	Tylenol with codeine
3	Materna
4	Motrin
5	ampicillin
6	amoxicillin
7	Monistat-7
8	tetracycline
9	Xanax
10	Ortho-Novum 1/35
11	Demerol
12	Ortho-Novum 7/7/7
13	erythromycin
14	Keflex
15	prenatal vitamins, unspecified
16	Bactrim DS
17	EES
18	Lo/ovral
19	Valium
20	Naprosyn
21	Darvocet-N 100
22	Amoxil
23	Septra DS
24	prednisone
25	Macrodantin

Source: National Disease and Therapeutic Index.

ANALEPTICS

Two analeptic drugs are marketed in the U.S. - methylphenidate (Ritalin^R), introduced in 1959, and pemoline (Cylert^R), introduced in 1975. Both are indicated for use in the treatment of attention deficit disorders, and methylphenidate is also indicated for narcolepsy.

Figure 3 shows the number of analeptic prescriptions dispensed by retail pharmacies from 1964 to 1986. The graph includes two data points for 1983, representing estimates derived from the original NPA projection methodology and the revised methodology introduced in 1983 (see section on Data Sources). Analeptic use peaked in 1971 at 4.4 million prescriptions and declined throughout the remainder of the 1970's. Prescription volume was relatively stable from 1980-1983 at around 1.5 million prescriptions. Estimates derived from the new projection methodology indicate that prescriptions for analeptics increased by 14% from 1983-1986, but remain at less than half of the 1971 peak level.

Methylphenidate accounts for a large majority of analeptic use, representing 88% of all analeptic prescriptions dispensed since the introduction of pemoline in 1975.

ANALEPTIC PRESCRIPTIONS 1964–1986

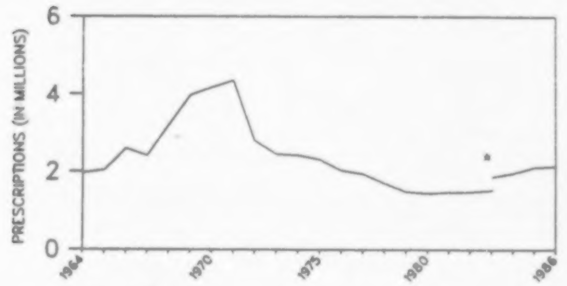

Figure 3

*Estimates for 1983 derived from the two NPA methodologies differed considerably, so both data points are displayed.

The profile of use for methylphenidate changed substantially from 1974 to 1986 (see Table 12). In 1974, methylphenidate was most commonly used by women (with 38% of NDTI mentions for females aged 20 and older), was most frequently prescribed by general or family practitioners and internists (42% of mentions), and almost one-third of its use occurred in the Midwest. By 1986, methylphenidate was most commonly used by male children (with 59% of NDTI mentions for males less than 20 years old, up from 30% in 1974) most frequently prescribed by pediatricians (46%, up from 18% in 1974), and almost one-third of its use occurred in the West (up from 17% in 1974). This changing profile reflects an increasing use of methylphenidate for "primary childhood behavior disorders" (the ICD7 term that would include attention deficit disorders) and decreasing use in the treatment of depression and neuroses.

Table 12. Profile of Methylphenidate Use

	1974	1978	1982	1986
Patient age/sex distribution (%)				
Males	52%	58%	63%	72%
0-9	18	21	22	34
10-19	12	13	17	25
20+	22	23	24	13
Females	48	42	37	28
0-9	5	5	2	9
10-19	4	3	7	4
20+	38	34	27	15
Prescriber specialty (%)				
Pediatrics	18%	14%	18%	46%
Psychiatry	21	29	39	22
GP/FP/IM	42	44	28	22
Neurology	7	7	11	5
Geographic region (%)				
East	23%	19%	34%	20%
Midwest	32	35	28	17
South	29	33	24	31
West	17	13	13	32
% Use for primary childhood behavior disorders	30%	39%	48%	70%

Source: National Disease and Therapeutic Index.

CYCLOSPORINE

Cyclosporine (Sandimmune^{R}) was approved for marketing by FDA in November 1983 as a new chemical entity representing an important therapeutic gain in immunosuppressive therapy. Official labeling indicates its use for the prophylaxis of organ rejection in kidney, liver, and heart transplants. The labeling also notes that because of the risk of anaphylaxis, the intravenous (IV) dosage form of cyclosporine should be reserved for patients who are unable to take the oral solution. Postmarketing cyclosporine use was first noted by the IMS America audits in December 1983.

Table 13 shows the trends in oral versus IV and ambulatory versus inpatient use of cyclosporine from 1984 to 1986. The percent changes in use between 1984, the first full year of marketing, and 1986 are also provided.

Intravenous use has been negligible, with IV dosage forms only representing about 1% of all cyclosporine purchased by drug stores and hospitals. Purchases of oral forms, however, more than tripled from 538 kgs. in 1984 to 1864 kgs. in 1986, with the greatest increase occuring in the outpatient environment. NPA data (not shown in Table 13) also show this increase in outpatient use, with dispensed precriptions (all for the oral form) increasing from 3,000 in 1984 to 93,000 in 1986. The increased movement of use from inpatient to outpatient is probably reflective of the transplant patient's need for long-term use of this drug.

Table 13. Trends in Cyclosporine Use by Dosage Form and Type of Patient

	1984		1985		1986		% Change
	Kg	%	Kg	%	Kg	%	1984-1986
Inpatient							
Oral	380	69	655	58	1100	58	189
IV	12	2	14	1	24	1	100
Ambulatory							
Oral	158	29	458	41	764	40	384
IV	1	<1	1	<1	1	<1	0
Total	551	100	1128	100	1889	100	243

Source: U.S. Pharmaceutical Market - Drug Store and Hospital Purchases.

PHENYLBUTAZONE

Phenylbutazone, approved by FDA in 1952, was the first prescription nonsteroidal antiinflammatory drug (NSAID) marketed in the U.S. The second prescription NSAID, oxyphenbutazone, was approved in 1960, followed by indomethacin and mefenamic acid in 1965. Five additional NSAIDs were approved from 1974 to 1978, and seven were approved in the 1980's.

Figure 4 shows trends from 1964-1986 in the total number of phenylbutazone prescriptions dispensed from retail pharmacies and the percentage that were new (rather than refill). From 1964 to 1974, prescription volume rose from 5.6 million prescriptions to 13.7 million prescriptions. Since 1974, the number of prescriptions has decreased annually. By 1986, phenylbutazone had declined to less than 7% of its peak level. The percentage of prescription volume that was for new prescriptions increased fairly steadily from 1964 to 1982, but has since remained relatively constant (77% in 1982 and 73% in 1986).

The rise and fall of phenylbutazone's popularity parallels the introduction of newer NSAIDs. Its use began to decline after ibuprofen was marketed (October 1974) and continued to decline with the introduction of additional NSAIDs. The 1983 imminent hazard petition filed by the Health Research Group for the removal of phenylbutazone from the U.S. market, along with its concomitant publicity and the more restrictive labeling resulting from FDA's review of the issues (cf Faich 1987[3]), may have contributed to the decline in phenylybutazone use, but the data show substantial annual decreases in prescription volume for most of the preceding decade.

PHENYLBUTAZONE PRESCRIPTIONS 1964–1986

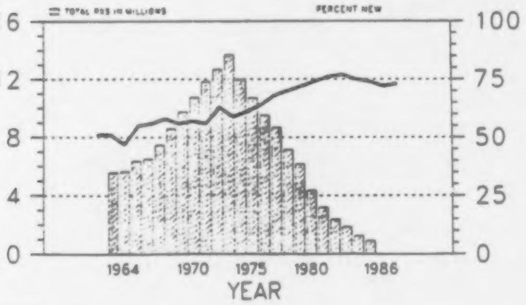

Figure 4

ISOTRETINOIN

Isotretinoin (Accutane^{R}), a retinoid which inhibits sebaceous gland function and keratinization, was approved by the FDA in May 1982 and introduced to the U.S market in August 1982. Isotretinoin represented a significant advance in the treatment of severe recalcitrant cystic acne; however, because of significant adverse events associated with its use, it is indicated only for cases of severe cystic acne that are unresponsive to conventional therapy. Isotretinoin is a potent teratogen, and its labeling carries a boxed warning on its contraindication in women who are pregnant or may become pregnant.

Retail pharmacies dispensed approximately 3.7 million isotretinoin prescriptions from 1982 to 1986. Figure 5 shows the annual number of prescriptions for each strength of isotretinoin. In 1982, 80% of the 251,000 prescriptions dispensed from retail pharmacies were for 40 mg. capsules. Despite the 1984 introduction of a 20 mg. dosage form, 40 mg. capsules still represent a large majority of isotretinoin use (76% of the 802,000 prescriptions dispensed in 1986).

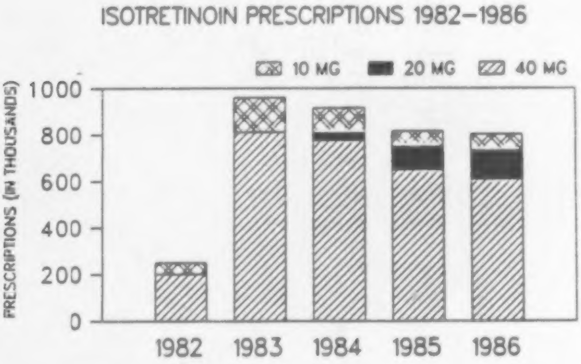

Figure 5

Total isotretinoin prescriptions peaked in 1983, the drug's first full year on the market. Decreased use in the following years may have been due to observations of human teratogenicity and reiterations of the warning against use in pregnancy from the manufacturer and in the medical literature; however, the percentage of isotretinoin used by women less than 40 years old has not decreased. In 1983, this group accounted for 40% of visits to private office-based physicians for isotretinoin therapy (see Table 14). In 1986, women under 40 accounted for 45% of such visits.

Table 14. Profile of Isotretinoin Use

	1983	1984	1985	1986
No. mentions (000)	827	692	617	656
% Rx'ed by				
Dermatologists	90	89	90	92
GP/FP/IMS	8	7	7	6
% New therapy	28	28	27	24
% Used alone	77	76	78	78
Patient age/sex distribution (%)				
Male				
0-19	22	28	26	27
20-39	34	24	25	24
40-59	1	2	1	3
Female				
0-19	8	12	12	13
20-39	32	31	33	32
40-59	4	3	3	2

Source: National Disease and Therapeutic Index.

ANTIDEPRESSANTS

Ten antidepressant drug entities were marketed in the U.S. throughout 1986. (An eleventh, nomifensine maleate, was withdrawn from the market by the manufacturer in January 1986 and is not considered here.) Retail pharmacies dispensed over 35 million prescriptions for these drugs in 1986 (see Table 15), a majority of which were for older drugs. Combination and single-entity forms of amitriptyline (introduced in 1961) represented 44% of all antidepressant prescriptions; doxepin (1969) and imipramine (1959) accounted for an additional 29%. Trazodone, a 1982 introduction, was the fourth most commonly dispensed antidepressant (10% of total).

Table 15. Antidepressants Marketed in the U.S. in 1986

Generic Name	Major Brand(s)	Year of Marketing	Million Rxs in 1986	% Antidepressant Rxs in 1986	Average Rx Size in 1986
Amitriptyline (single entity)	Elavil Endep	1961 1975	10.1	28	56
Amitriptyline (combinations)	Triavil Limbitrol Etrafon	1965 1978 1964	5.7	16	62
Amoxapine	Asendin	1980	0.9	3	53
Desipramine	Norpramin Pertofrane	1975 1971	2.1	6	57
Doxepin	Sinequan Adapin	1969 1973	5.6	16	52
Imipramine	Tofranil	1959	4.5	13	63
Maprotiline	Ludiomil	1981	1.1	3	57
Nortriptyline	Pamelor Aventyl	1977 1964	1.3	4	66
Protriptyline	Vivactil	1967	0.3	1	64
Trazodone	Desyrel	1982	3.6	10	51
Trimipramine	Surmontil	1979	0.3	1	55
Total			35.6	100	

Source: National Prescription Audit.

Figure 6 shows trends in prescription volume from 1964 to 1986. Except for a decrease in the number of prescriptions from 1975 to 1979 and a slight drop in 1984, antidepressant use has risen steadily over the 23-year period. Amitriptyline has been the most commonly used antidepressant since 1965, with substantial variation in its use in single-entity vs. combination products. From 1968 to 1975, a majority of amitriptyline was used in combination form. Since 1976, single-entity amitriptyline has been the more commonly used form. Only 36% of amitriptyline prescriptions were for combination products in 1986.

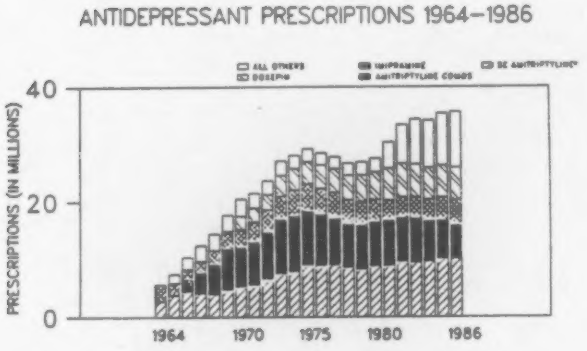

Figure 6

Tables 16-18 provide data from the nonhospital NDTI. Tables 16 and 17 do not list protriptyline and trimipramine separately as their use was too infrequent to allow adequate estimation of most of the variables on these tables; however, protriptyline and trimipramine data are included in the antidepressant totals.

Table 16 shows the age and sex distribution of outpatients receiving antidepressants. Women are the predominant users, representing 69% of all antidepressant mentions reported in the 1986 nonhospital NDTI. For the individual antidepressants, the percentage of users that were women ranged from 62% for imipramine to 79% for amoxapine.

Antidepressants were rarely prescribed for patients less than 20 years old. Imipramine was the exception, with 14% of its use in this age group (probably reflecting its indication for childhood enuresis). Three-quarters of antidepressant users were between 20 and 64 years old, and approximately 22% were 65 or older. The highest proportion of use in the elderly was observed for amitriptyline and doxepin.

Table 16. Age and Sex Distributions of Antidepressant Users, 1986

			Percent in Age Group			
	% Male	%Female	0-19	20-39	40-64	65+
Amitriptyline						
Single-entity	31	69	2	30	38	30
Combinations	27	73	*	24	47	28
Amoxapine	21	79	*	26	47	26
Desipramine	30	70	4	37	47	12
Doxepin	29	71	*	27	43	30
Imipramine	38	62	14	35	38	13
Maprotiline	29	71	*	31	46	21
Nortriptyline	29	71	*	36	39	22
Trazodone	32	68	*	31	44	23
All Antidepressants	31	69	3	31	44	22

Source: National Disease and Therapeutic Index (Nonhospital), 1986.

*Insufficient data for adequate estimation.

The nonhospital NDTI reported that the three diagnoses most commonly associated with the use of antidepressants were neurotic depressive reaction (40% of all antidepressant mentions), manic depressive reaction (16% of mentions), and anxiety reaction (4% of mentions). A variety of other diagnoses were associated with 2% or less of the mentions: two percent of single-entity antidepressant mentions were for ICD7 diagnoses of other pathological personality, depressive reaction, obsessive compulsive disorder, or other character disorder. Seven percent of imipramine mentions were for incontinence of urine.

As shown in Table 17, the percent of mentions used for neurotic depressive reactions ranged from 33% for single-entity amitriptyline to 53% for trazodone. Neurotic depressive reactions also accounted for a majority of maprotiline and trazodone use. Use for manic depressive reactions ranged from 6% for combination amitriptyline products to 32% for desipramine.

Prescribing by physicians with specialties in general practice, family practice, or internal medicine accounted for 43% of antidepressant mentions and psychiatrists accounted for 41% (see Table 18). Psychiatrists accounted for a majority of mentions for desipramine (68%), nortriptyline (64%), and imipramine (59%).

Antidepressant products were slightly more likely to be used alone (54%) than with other drugs, and 23% of their use was for new rather than continuing therapy.

Table 17. Antidepressant Therapy, 1986

	Associated Diagnoses (% of Mentions)			Percent Prescribed by			
	Neurotic Depressive Reaction	Manic Depressive Reaction	Anxiety Reaction	GP/FP/IM*	Psychiatrist	%Used Alone	%New Therapy
Amitriptyline							
Single-entity	33	8	3	50	26	52	24
Combinations	38	6	11	60	22	60	21
Amoxapine	52	15	**	46	37	53	29
Desipramine	40	32	**	22	68	53	21
Doxepin	42	11	5	49	36	51	26
Imipramine	35	19	9	25	59	61	17
Maprotiline	61	18	**	43	46	57	25
Nortriptyline	43	28	**	24	64	49	21
Trazodone	53	17	3	45	41	56	24
All antidepressants	40	16	4	43	41	54	23

Source: National Disease and Therapeutic Index (Nonhospital).

* General practice, family practice, or internal medicine.

** Insufficient data for adequate estimation.

Table 18 compares antidepressant use with the use of monoamine oxidase (MAO) inhibitors and lithium. MAO inhibitors and lithium are used by a younger population, are used more frequently for manic depressive reactions than neurotic depressive reactions, and are prescribed predominantly by psychiatrists. A very low percentage of NDTI mentions for these drugs were for new therapy, but this may partially reflect the need for closer monitoring of patients taking these drugs (with a proportionally greater number of physician visits by patients maintained on MAO inhibitors and lithium). Compared with antidepressants and MAO inhibitors, lithium was more likely to be used by men and less likely to be used as the only drug therapy. The drugs most frequently used with lithium were cyclic antidepressants (21% of lithium mentions) and phenothiazine antipsychotics (18%).

Antidepressants are used much more extensively than MAO inhibitors or lithium. While retail pharmacies dispensed over 35 million prescriptions for antidepressants in 1986, they dispensed only 2.8 million prescriptions for lithium and 0.6 million prescriptions for MAO inhibitors.

Table 18. Profile of Use for Antidepressants, MAO Inhibitors, and Lithium, 1986

	Antidepressants	MAO Inhibitors	Lithium
Patient age and sex			
Percent male	31	30	43
Percent female	69	70	57
Age group (%)			
0-19	3	*	*
20-39	31	54	46
40-64	44	32	42
65+	22	14	9
Associated diagnoses (Percent of total mentions)			
Neurotic depressive reaction	40	29	7
Manic depressive reaction	16	38	65
Anxiety reaction	4	8	*
Percent prescribed by physician specialty			
General/family practice	23	*	5
Internal medicine	20	*	6
Psychiatry	41	84	81
Percent used alone	54	55	38
Percent with benzodiazepine tranquilizers	15	22	8
Percent new therapy	23	7	5

Source: National Disease and Therapeutic Index (Nonhospital).

* Insufficient data for adequate estimation.

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2. U.S. Bureau of the Census. Estimates of the population of the United States, by age, sex, and race: 1980 to 1986. (current population reports, series P-25, No. 1000).
3. Faich GA. Risks and indications of phenylbutazone: Another look. Pharmacotherapy 1987, 7:25-7.

APPENDIX A

Bibliography of Selected Drug Use Publications, 1986

Article	Data Source	Study Location	Period Surveyed
Bates WJ, Smeltzer DJ, Arnoczky SM. Appropriate and inappropriate use of psychotherapeutic medications for institutionalized mentally retarded persons. Am J Ment Defic 1986;90:363-70.	Summaries of multidisciplinary evaluations of 242 patients in 5 states institutions	OH	Late 1970s?
Benson PR. The prescription of discretionary antipsychotic medication by state mental hospital psychiatrists. J Health Soc Beh 1986;27:28-43.	Survey of 63 staff psychiatrists in 2 hospitals (26 respondents; 21 or 22 plus 5 psychiatric residents analyzed); chart review of 584 patients (557 analyzed)	NC	1979
Cochi SL, Flemming DW, Hull HF et al. Haemophilus influenza polysaccharide vaccine. Physician acceptance and use of a new vaccine. Am J Dis Child 1986; 140:1226-30	Survey of 585 physicians (565 respondents, 369 analyzed)	NM	1985
Dasta JF. Drug use in a surgical intensive care unit. Drug Intell Clin Pharm 1986; 20:752-6.	Medical records of 180 patients admitted to a surgical intensive care unit.	OH	1984
Davidson RA, Meuleman JR. Initial treatment of hypertension: A questionnaire survey. J Clin Hypertens 1986;2:339-45.	Survey of 144 physicians (95 respondents)	FL	?
Gallup GJr, Cotugno HE. Preferences and practices of Americans and their physicians in antihypertensive therapy. Am J Med 1986; 81(Suppl 63):20-4.	2 surveys: 300 physician respondents, 500 hypertensive patients.	US	1986
Groves JB, Batey SR, Wright HH. Psychoactive drug use among adolescents with psychiatric disorders. Am J Hosp Pharm 1986;43:1714-8.	Medical records of 204 adolescents admitted to a psychiatric hospital	SC	1974-84

Haggerty JJJr, Evans DL, McCartney CF, Raft D. Psychotropic prescribing patterns of nonpsychiatric residents in a general hospital in 1973 and 1982. Hosp Community Psychiatry 1986;37:357-61	Charts of all patients in one hospital receiving psychotropic drugs (1973 n=1361; 1982 n=2648)	NC	7/73-8/73; 2/82-4/82
Higgins JE, Chi IC, Wilkens LR, Hatcher RA. Patterns of depo-provera use in a large family planning clinic in the United States. J Biosoc Sci 1986;18:379-86.	Computerized records of 36,298 black women aged 10-49 (1967 n=5253; 1976 n=11,150)	GA	1967-76
Hlatky MA, Fleg JL, Hinton PC et al. Physician practice in the management of congestive heart failure. J Am Coll Cardiol 1986;8:966-70.	Survey of 5830 physicians (2704 respondents)	US	1984
Larrat EP, Mattea EJ. Pain cocktails: Survey of formulations used in U.S. hospitals. Hosp Formul 1986;21:497-9,502-3.	Survey of 1000 hospitals and clinics (386 respondents, 14 with incomplete responses)	US	?
Maiman LA, Becker MH, Katlic AW. Correlates of mothers' use of medications on their children. Soc Sci Med 1986;22:41-51.	Survey of 500 mothers presenting at 2 pediatric ambulatory care sites for a well child visit.	NY	9 mos ?
Ray WA, Schaffner W, Federspiel CF. Differences between female and male children in the receipt of prescribed psychotropic and controlled-analgesic drugs. A five-year epidemiologic study. Med Care 1986;24:801-13.	Computerized records of 341,422 children enrolled in a Medicaid program	TN	1977-84
Ray WA, Schaffner W, Oates JA. Therapeutic choice in the treatment of hypertension. Initial treatment of newly diagnosed hypertension and secular trends in the prescribing of antihypertensive medications for Medicaid patients. Am J Med 1986; 81 (Suppl C): 9-16.	Computerized records of (1) 4418 patients enrolled in Michigan Medicaid and (2) prescriptions reimbursed by Tennessee Medicaid	MI TN	1982-83 (MI); 1983-86 (TN)
Remington PL, Rowley D, McGee H et al. Decreasing trends in Reye syndrome and aspirin use in Michigan, 1979 to 1984. Pediatrics 1986;77:93-8	Survey of 199 families with children less than 18 yrs old; review of Reye syndrome cases	MI	1979-84

Schechter NL, Allen DA, Hanson K. Status of pediatric pain control: Comparison of hospital analgesic usage in children and adults. Pediatrics 1986;77:11-5.	Medical records of 90 children and 90 adults from 2 hospitals	CT	3yrs. ?
Steur BA, Dean BS, Everson GW, Krenzelok EP. Syrup of ipecac availability: Before and after a poisoning. Vet Hum Toxicol 1986;28:65-6.	Review of 1230 poison exposure cases; survey of 150 cases	PA	1984-85
Zimmer JG, Bentley DW, Valenti WM, Watson NM. Systemic antibiotic use in nursing homes. A quality assessment. J Am Geriatr Soc 1986;34:703-10.	Medical records of 2238 patients in 42 long-term care facilities	NY	1983

Item 18

RESEARCH & REPORTS

ASSESSING THE IMPACT OF A DRUG-HOLIDAY PROGRAM

William Simonson,
Karen Schaefler, and
Robert Williams

Abstract: The implementation of a drug-holiday program in a 137-bed intermediate-care facility was evaluated.

Before beginning the routine omission of selected drug doses, physicians, nurses, and patients in the nursing home were informed of the purpose, benefits, and risks of a drug-holiday program. Baseline demographic data and relevant laboratory-test results were recorded for four weeks before the drug-holiday program began. Doses were omitted on Tuesdays, and relevant data were recorded on Tuesdays and Wednesdays of each of the 13 weeks during the study period.

Data for the 55 patients who completed the study indicated that patient behavior was more stable during the drug-holiday period. Use of as-needed pain medications changed significantly during the period, with some patients taking more and others less. Patients who had laxatives withheld did not require more laxatives on the following day during the drug holiday, and patients whose psychotropic medications were omitted had no significant changes in behavior. Those omitting doses of diuretics or potassium supplements altered their use of as-needed pain medications. No significant results were found in patients whose omitted medications included antihypertensive agents or digoxin.

No detrimental effects were identified in patients receiving a drug holiday; use of as-needed pain medications changed but not in a consistent direction.

A drug holiday is a scheduled or periodic omission of one or more of a patient's prescribed medications. The successful implementation of drug holidays has been reported in patients with Parkinson's disease who had become refractory to the therapeutic effect of levodopa. Following temporary discontinuation of this drug, many of these patients experienced considerable improvement when levodopa therapy was reinstituted.[1-3]

The drug holiday has also been used in patients with psychiatric disorders such as schizophrenia to decrease unnecessary psychotropic use and drug toxicity.[4-10]

The practice of occasional or routinely scheduled drug holidays has been tested in various health-care environments, but the greatest utility of a drug holiday appears to be with nursing home patients.[11-13] Most studies that have investigated medication-consumption patterns of elderly nursing home residents have concluded that this population is frequently the victim of overprescribing, polymedicine, and inappropriate medication use.[14]

Drug holidays can, in fact, decrease the consumption of drugs in nursing home patients. However, patients have not been evaluated systematically to determine whether the temporary discontinuation of specific prescription or nonprescription drugs has a negative impact on the condition of the patients or the cost of their drug therapy. There is no argument that medications are frequently misused and overused in the elderly population, but appropriate drug therapy undoubtedly improves both the health and quality of life of many elderly patients.

When used in the nursing home environment a drug holiday should be looked at not as an "end" but rather should be considered a "means" to help identify medications that are either unnecessary or inappropriate. The drug holiday, therefore, represents just one step in what should be a constant effort to encourage the appropriate use of medications in elderly patients.

Methods

The study was conducted in a 137-bed intermediate-care facility in Portland, Oregon.

Implementation of the drug-holiday program involved a great deal of planning by physicians, professional nursing staff, and the con-

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Criteria	Explanation
Alert and oriented × 1	Ability to state one's name
Alert and oriented × 2	Ability to find one's room
Alert and oriented × 3	Ability to get to meals with reminders from staff
Wandering	Behavior that resulted in or would result in patient leaving facility if left unrestrained
Abusive	Physical and verbal abuse
Anxious	Oral expressions of feeling nervous or jittery Increase in somatic complaints such as upset stomach or tension Physical manifestations such as pacing
Depression	Withdrawal Decrease in communication and verbalization
Change in sleeping pattern	Increase in restlessness Use of seldom-needed sleeping medication Quieter than usual at night
Loud, lethargic, cooperative, restless, bowel incontinence	Self-explanatory

Table 1. Observation Criteria for Patients on Drug Holidays

sultant pharmacist. Much of the available literature pertaining to drug holiday was reviewed; other facilities already involved in drug-holiday programs were visited. Finally, facility policy and evaluation forms were developed. This policy included a procedure for starting a patient on a drug holiday, criteria for including newly admitted patients and newly ordered medications into the program, and recommendations about drugs that were believed inappropriate for inclusion in the drug holiday.

The consultant pharmacist provided input in this phase of the study, especially in deciding which medications could be safely withheld. The evaluation forms were designed so that data could be collected and analyzed regarding use of specific routinely scheduled and p.r.n. medications, changes in blood pressure, patient behavior, bowel patterns, and changes in orientation.

The primary physician for each patient in the study facility was sent a letter by the consultant pharmacist explaining the proposed drug-holiday program along with copies of the policy and procedures, patient-evaluation form, and current patient-medication profile. Participation was solely at the discretion of the patient's physician, who could order that some or all of their patients' medications be withheld for one day each week during the study period.

Nursing and pharmacy staff and medication aides were fully informed of the rationale and goals of the program as well as the proper method of data collection.

Baseline laboratory values for digoxin, potassium, theophylline, and hemoglobin were determined in the two months before the drug holiday, and follow-up values were determined either in the final month of data collection or in the subsequent month. Patients were selected for these laboratory studies based on which medications were to be withheld and on what their previous laboratory schedules had been.

Data were collected for two days each week by professional nurses and medication aides. The days chosen were Tuesday (the drug holiday) and Wednesday. The aides collected objective data regarding each participant's use of sleeping medication, p.r.n. pain medication, and laxative use on these days. They were also asked to check and record the blood pressure of patients whose antihypertensive medications were withheld. These blood pressures were also obtained on Tuesday and Wednesday of each week.

Nurses collected data on bowel incontinence, degree of orientation, and behavior patterns for the same two-day period. Before beginning the data collection, criteria were established for determining the presence or absence of each behavior (Table 1).

The evaluation forms were filled out on Tuesday and Wednesday for the four weeks of baseline and the first 13 weeks of the drug-holiday study period. This was done to obtain information on the day that medications were withheld and on the following day. In this way delayed effects of withholding medications secondary to lower serum concentrations would be detected as well as more immediate effects. Each patient served as his own control.

Because of staff scheduling, each patient could potentially be evaluated by three different staff members at most throughout the data-collection period. During the 17-week period, we believed that variations in individual evaluation of behaviors would be negligible, but space was provided on each form for comments if an evaluator wanted to expend on an answer to a particular question.

During the four weeks of initial evaluation (before actually withholding medications) all existing orders for all patients participating in the drug holiday were retyped to include the physician's order authorizing participation in the program and to note any exemptions specified by the physician. This became part of the patient's permanent record and was carried forth each month. Medications to be withheld were appropriately noted on the patient profile to facilitate identification by all staff members.

In the week just before the initial drug holiday, individual discussions were conducted with those patients whom the staff believed would be particularly concerned with the periodic omission of some of their medications. The program was explained, and assurance was given that their physicians had approved participation. Some minor changes were made to reflect particular patient concerns. In every case, the patient agreed to give the program a try and no problems were encountered. Patients who were not alert or oriented were included in the study only if their physicians believed that inclusion would benefit the patients.

The program was also reviewed with the entire staff of the facility and the pharmacist before implementation. Everyone was asked to note any changes in behavior and report those to the nurses.

A colored highlighter pen was used on the medication-administration record to mark every Tuesday for those drugs being withheld. This technique made the drugs to be withheld and the day to withhold them clearly apparent to all those administering medications.

Data were collected in five general areas for all patients in the study: (1) use of sleeping medication, (2) use of p.r.n. pain medication, (3) use of laxatives, (4) bowel incontinence, and (5) changes in degree of orientation. Additionally the following behavioral patterns were assessed: (1) alert and oriented, (2) cooperativeness, (3) anxiety, (4) depression, (5) loudness, (6) abusiveness, (7) wandering, (8) restlessness, (9) lethargy, and (10) sleep patterns.

Student's *t* tests for paired data were performed on both the directional data and the data reflecting the occurrence of change. The level of significance was $p < 0.05$. The total sample was evaluated for significant behavior changes in the preholiday versus the holiday period. To determine if withholding medications from specific pharmacologic categories was a factor, subgroups of patients who had laxatives, psychotropic agents, diuretic agents, potassium supplements, or vitamin-mineral supplements withheld were analyzed separately. These groups were chosen because they were the only groups with enough patients from which to draw statistically significant conclusions.

To determine if there were age-related changes, an analysis was done for those 80-89-year-old patients who had psychotopic drugs withheld. Major diagnoses were analyzed to find any changes that could be related to medical condition.

Blood pressure changes were evaluated for significance in two ways: (1) changes occurring between the four-week preholiday period and the 13-week holiday period; and (2) changes occurring between the drug holiday and the following day to detect more subtle fluctuations in pressure readings. The use of p.r.n. pain medications by those patients having anti-inflammatory medications withheld was analyzed for changes. Patients in whom routine laxatives were withheld were evaluated for changes in their use of p.r.n. laxatives, both

Medication Class	No. Meds/Class
Vitamins/minerals	34
Diuretics	14
Cardiotonics	8
Antihypertensive agents	6
Potassium supplements	12
Laxatives/softeners	22
Major tranquilizers	22
Miscellaneous agents*	34

*Miscellaneous medications included nonsteroidal anti-inflammatory agents, minor tranquilizers, histamine H^2 blockers, analgesics, antacids, antidepressants, anticholinergics, and respiratory agents.

Table 2. Classes of Medications Withheld During the Drug Holiday

Under 60 years	3 (5.5%)
60-69 years	7 (12.7%)
70-79 years	6 (10.9%)
80-89 years	31 (56.3%)
90-99 years	8 (14.5%)

Table 3. Age Distribution of 55 Patients Completing Study

the day after the laxative was withheld and in the previous week to determine any longer-term effects.

The final analysis performed involved checking for significant changes in serum concentrations of digoxin, potassium, and hemoglobin following three months of weekly withholding of digoxin, potassium supplements, and vitamin-mineral supplements, respectively.

Results

A total of 20 physicians were informed of the study and asked to participate, and six accepted for at least some of their patients. A total of 55 patients completed the study and were included in data analysis. Information about the patients and their medications is in Tables 2-4.

As the program progressed, additional patients were included, some were discharged, and others died. Similarly, medications were added or deleted, and dosage adjustments were made.

With two exceptions, only those patients who were in the facility for the full four months were included in the data analysis. The two exceptions were patients who spent a brief time in the hospital and were returned to the facility. A third patient was in the facility for the full four months, but was not added to the holiday program until the first week medications were actually withheld; thus, data were available only for the final 13 weeks on this patient.

The medications included in the analysis were only those that were consistently withheld throughout the final 13 weeks of the data collection (i.e., that time period for which medications were actually withheld). Only those laboratory values obtained during the four-month study period and the month before or following that time period were included for analysis. The serum theophylline concentration determined was not included in the data analysis, since the drug was only withheld in one patient.

Results for all Patients: For all 55 patients completing the study, the use of p.r.n. pain medications changed significantly between the preholiday period and the holiday period. Fewer changes were noted from Tuesday to Wednesday in the four-week period preceding the drug holiday than during the 13-week drug-holiday period itself, but when directional data were analyzed, the change lost significance. This indicates that during the drug-holiday period patients were increasing their use of p.r.n. pain medications while others were decreasing their use. This change is thought to have had no clinically important effect on any patient.

Other parameters that showed significant changes in the total sample were "alert and oriented times 1," with fewer patients showing day-to-day changes during the drug-holiday period, and degree of loudness, again with fewer patients showing day-to-day changes during the drug-holiday period. In other words, the data indicate that patient behavior was somewhat more stable during the drug-holiday period, although the clinical relevance of this change appeared to be negligible.

Results in Patients Receiving Laxatives: In the study, 22 patients had routine laxatives withheld. These included stool softeners, cathartics, and bulk agents. The only significant change noted was in the use of p.r.n. pain medication from the preholiday to the drug-holiday period. More patients altered their use of p.r.n. pain medications during the drug-holiday period than in the pre-holiday period. Directional data were not significantly different between the two periods. This indicates that, while a significant change occurred, neither increased or decreased use was predominant.

A separate analysis was performed specifically correlating laxative use for the week before the day medications were withheld, the drug holiday, and the day following drug holiday. There was no significant change in patients' use of laxatives between the preholiday period and the holiday period either on the next day or in the previous week. There was a highly significant change in laxative use on the drug-holiday day itself—but this obviously reflects the fact that medications (including laxatives) were withheld that day as opposed to any true difference in laxative consumption.

Results in Patients Receiving Psychotropic Agents: A total of 22 patients had a psychotropic medication withheld once weekly. Drugs in this category included haloperidol (Haldol, McNeil Pharmaceutical), thioridazine (Mellaril, Sandoz Pharmaceutical Division), chlorpromazine (Thorazine, Smith Kline & French), trifluoperazine hydrochloride (Stelazine, Smith Kline & French), diazepam (Valium, Roche Products), and chlorazepate dipotassium (Tranxene, Abbott). There were no significant changes in any of the study variables between the two time intervals.

Effects of Age: As renal and hepatic function decline with age, changes in the efficacy of the psychotropic agents would more likely occur as age increases. In an effort to determine whether this was the case, those patients 80-89 years old were analyzed for behavior changes. Changes in the use of p.r.n. pain medications did become significant, with fewer changes occurring in the predrug-holiday period. Directional data showed a similar trend in this age group as for the whole sample. The degree of bowel incontinence also changed significantly, with fewer changes occurring in the drug-holiday period. This implies that bowel habits were more stable during the drug holiday than previously, although patients did not become more or less incontinent according to directional data.

No other parameters showed significant changes in this age group. Thus, age does not seem to play a major role in the degree of change seen when withholding psychotropic drugs.

Results in Patients Receiving Diuretic Agents: A total of 14 patients had some type of diuretic withheld; no attempt was made to separate those for whom diuretics were prescribed as agents to control blood pressure and those who were taking diuretics for edema control.

Use of p.r.n. pain medication was again the only category with a significant change. More change was seen during the drug holiday, but this difference disappeared when directional data were analyzed.

Results in Patients Receiving Potassium Supplements: A total of 12 patients had potassium supplements withheld; 10 of these also had a diuretic held while two had only their potassium withheld. The only significant change was seen with the use of p.r.n. pain medication. More people exhibited a change in their use of p.r.n. pain medications during the drug-holiday than during the preholiday period; no directional significance was noted. All other categories of analysis had no significant changes.

Results in Patients Receiving Antihypertensive Medications: Changes in blood pressure were of concern in those patients who were receiving cardiac, antihypertensive, or diuretic medications. Because isolated systolic hypertension is a serious problem in the elderly, both systolic and diastolic pressures were analyzed in the patients having the aforementioned medications withheld. To eliminate day-to-day normal fluctuations in blood pressure from the analysis, only changes of 10 mm Hg or greater were recorded; this change could represent either an increase or a decrease in pressure readings.

Of the eight patients who had cardiac drugs withheld, no significant changes occurred in either systolic or diastolic pressures. The same result was seen for the six patients in whom antihypertensive drugs and diuretics were withheld.

Effects on Serum Digoxin Concentrations: Serum digoxin concentrations were determined during the month before the drug holiday and in the third or fourth month after medications were withheld for patients having digoxin withheld. Samples were drawn six to eight hours after the medication was administered.

No statistically significant changes were seen and all values remained within the therapeutic range.

Effects on Serum Chemistry Values: Serum potassium concentrations and hemoglobin values were determined during the month before the drug holiday and in the third or fourth month after medications were withheld. No statistically significant changes occurred.

Financial Analysis: All medications withheld during the drug-holiday period were recorded to determine the cost savings resulting from decreased medication use. The number of medications withheld per patient averaged 3.30 for the 55 patients studied and ranged from a maximum of 10 to a minimum of 1.

The cost of the medications being withheld was calculated based on the medication and frequency of use. All costs are stated as a function of the medications' average wholesale prices as listed in the December 1984 *Redbook* update published by Medical Economics Company.

The maximum savings for any patient during a one-week period was $3.17 and the minimum was $0.06. The average saved was $0.76 per patient per week, which would be equivalent to an annual savings of $39.52 per patient.

Cardiovascular disease	12 (21.8%)
Diabetes mellitus	2 (3.6%)
Cerebrovascular accident	8 (14.5%)
Dementia	17 (30.9%)
Neurologic disorders	7 (12.7%)
Other (includes anemia, arthritis, mental illness, gastrointestinal disorders)	9 (16.4%)

Table 4. Major Diagnoses of 55 Patients Completing Study

Discussion

Several potential benefits can be derived from a systematic, well-organized, and properly evaluated drug-holiday program. These advantages include the identification of medications that may be causing adverse drug reactions and drug interactions, identification of unnecessary medications, decreased expenditures resulting from decreased medication consumption, reduction of nursing time involved with drug administration, and decrease in pharmacist time involved with drug formulation, packaging, and dispensing.

The drug-holiday concept can help to identify some types of unnecessary medications. Thus, the implementation of a drug-holiday program may help to refute the adage "once digoxin, always digoxin," and the notion that hypertensive patients will have to take their blood-pressure medications "forever."

For example, some studies have demonstrated that digoxin can be safely discontinued in many patients who have been taking the drug. Some patients who are taking digoxin were originally given the drug inappropriately, perhaps as the result of a misdiagnosis. Also, digoxin may be relatively ineffective in many patients with congestive heart failure.

Since continuous drug therapy may be unnecessary in many patients with hypertension,

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especially those with mild hypertension,[17] certain antihypertensive agents might be discontinued following a lack of blood-pressure changes during a drug holiday.

The reduction of unnecessary medications may also contribute greatly to the reduction of adverse drug reactions and drug interactions. This may be especially true in the elderly, since the incidence of adverse reactions is increased in this population. Commonly used drugs such as digoxin may cause serious problems such as confusion, depression, anorexia, and visual disturbances, while diuretics, which are usually considered to be very nontoxic, may result in numerous problems in the elderly including fainting, orthostatic hypotension, weakness, and gout.

A sufficient number of patients in this study were consuming laxatives, psychotropics, diuretics, potassium supplements, and vitamin-mineral supplements to allow a statistical analysis of the effect of withholding these medications on patient status. The effect of withholding medications from additional pharmacologic categories was also assessed, since a comparison of all patient-related data was made between the preholiday and drug-holiday period. Minor statistical changes were observed indicating that patients may have actually been more stable during the drug-holiday period, since fewer changes in patient orientation and degree of loudness were noted during that time. We believe, however, that these changes are of no clinical relevance.

The drug-holiday program described is continuing at the facility with few changes. The staff remains alert to the possibility of undesirable drug effects, and patients in the facility are routinely being evaluated for possible inclusion in the study.

Adequate preparation and communication are essential when establishing a drug-holiday program. A clearly written policy must be developed, and all facility staff must be completely familiar with the program. Physicians must be informed of the program and must be permitted to have sufficient input as the program guidelines are developed. Before its implementation, the program must be explained to patients and family members so that they may understand the benefits to be gained. This explanation may also help to reduce the anxiety that may occur when an expected medication is not administered.

While we did not record the exact amount of time required to set up this program, we estimate approximately eight hours of pharmacist time and 20 hours of nursing time were required. Most of this time was devoted to policy development and staff in-service education, making it a one-time expense. A portion of this time was devoted to planning the procedures and methods required for this study. Some of this time would, therefore, not be required when setting up a drug-holiday program that did not have a formal evaluation component.

Patients selected for inclusion in the program must be chosen with care. Criteria to be considered are types of medications ordered, overall health status, lability of present condition, and ability of staff to monitor for changes in condition.

The benefits of a drug-holiday program have previously been identified. In this study, a well-designed drug-holiday program had no detrimental effect on participating patients. Nursing homes that are not currently coordinating such programs should consider doing so. However, the primary motivation must be improved patient care, not decreased nursing time or cost savings.

Conclusion

A drug-holiday program had no detrimental effect on study patients. Some statistically significant changes in patient behavior were noted when comparing the preholiday period with the drug-holiday period. The use of p.r.n. pain medications appeared to change when comparing the preholiday with the drug-holiday period. The change lacked both noticeable direction and strong statistical significance, so it may well have been a random change.

Nursing homes that are offering drug-holiday programs should consider doing so as one way of identifying unnecessary medications and other medications that may be causing problems. ☐

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Item 19

TRENDS & ANALYSIS

COST-BENEFIT OF PHARMACIST-CONDUCTED DRUG-REGIMEN REVIEWS

Samuel W. Kidder

Abstract: The published literature and other studies are reviewed and the national impact assessed on cost-benefit of pharmacist-conducted drug-regimen review in skilled-nursing facilities.

A total of 23 studies, most published in peer-reviewed journals, are available. The studies show decreases in number of medications prescribed per patient, nursing time spent on drug administration, hospitalizations, cost of medications, and antipsychotic-drug use during periods of pharmacist review.

Estimated national savings from pharmacist-conducted drug-regimen review were based on reduced drug use, averted hospitalizations, and reduced drug-administration time. Medicare and Medicaid did not have to pay for 0.7 refills per patient-month in the latest year for which data are available, or 7.49 million prescriptions at a cost of $81 million. A saving of $224 million resulted from decreased hospitalizations attributable to drug-regimen review. About $154 million in reduced nursing time could be saved from pharmacists' activities, although most of the saved time would be used for enhanced nursing activities. The net saving from pharmacist-conducted drug-regimen review was calculated at $220 million.

Studies conducted to date provide convincing evidence of pharmacists' effectiveness in ameliorating drug-therapy problems in skilled-nursing facilities.

The Department of Health and Human Services on June 15, 1987, promulgated final regulations recognizing the pharmacist as the professional of choice for conducting drug-regimen reviews in intermediate-care facilities (ICFs).[1] Before this regulation, pharmacists were designated to conduct reviews only in skilled-nursing facilities (SNFs); registered nurses were designated in ICFs.

This change was stimulated by a proposed rule published in the May 16, 1986, *Federal Register*[2] that would have designated either the pharmacist or the nurse as the reviewer in both ICFs and SNFs. This rule would have allowed greater flexibility for the facility in choosing who should be designated to conduct the reviews. But public comments were in opposition to this flexibility, preferring instead to designate the pharmacist in both settings.

Pharmacy, nursing, consumers, and nursing home organizations were united in their support of the pharmacist in both settings. They all believed that registered nurses did not have the time and that pharmacists had a better knowledge base for this function. The wisdom of this public-health decision has been borne out by many experiences and studies all across the country. In this paper, I will review the published literature on the cost-benefit of pharmacist-conducted drug-regimen review and attempt to extrapolate from these data to estimate the nationwide effect of this valuable pharmacist service.

Published Literature

Before delving into an analysis of the available studies on pharmacist-conducted drug-regimen review, I should note some of the inherent limitations to this research. Most of the studies presented are small and geographically restricted. Some do not follow a randomization process, thus weakening their external validity. Also, most studies do not analyze quality of care, so a reduction in number of prescribed drugs does not necessarily mean an improved quality of care. I would argue, however, that the physicians who must implement all pharmacists' recommendations have quality of care foremost in their minds. Table 1 summarizes studies showing reductions in prescription drug use as a result of pharmacist-conducted drug-regimen review. A total of 23 studies, most published in peer-reviewed journals, are

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available that demonstrate a reduction in drug use or other drug-therapy improvements. Below is a short summary of each study complementing the information in Table 1.

CHEUNG AND KAYNE.[3] Medication errors were reduced from 20% to 8% in this 11-month study of 517 patients. A total of 122 adverse drug reactions were detected or prevented, 68 of them clinically significant. The researchers estimated that 68 hospitalizations were avoided, thereby averting $49,000 in costs, and the average number of prescriptions per patient was reduced from 6.8 to 5.6.

RAWLING AND FRISK.[4] These researchers showed an average reduction in drug orders from 7.7 to 6.1 per patient during 4.5 years of consulting to three Idaho nursing homes. The average monthly drug costs per patient dropped from $28.89 to $26.30, saving $673.40 per month and $8,080 per year for all patients.

ELLENOR AND FRISK.[5] Table 2 outlines the effects of two years of drug monitoring in an Idaho ICF for the mentally retarded housing 475 residents. The cost savings were estimated at $10,000.

HOOD ET AL.[6] In a controlled study, Hood et al. monitored 27 test patients and 25 control patients for two months. The test group's average prescriptions per patients fell by 0.9, compared with 0.2 in the test group.

MARTTILA.[a] In an unpublished study, Martilla conducted drug-regimen review for 20 randomly selected patients. He was able to demonstrate an average reduction in drug orders per patient from 7.2 to 5.6.

LOLHOLM.[7] Cost savings of $0.40 per day resulted from interventions in this 13-month study of 55 SNF patients in 1977. Average drug use went from 6.8 to 4.4 prescriptions per patient.

COOPER AND BAGWELL.[8] In this 1976 study of 142 patients in a Georgia SNF, Cooper and Bagwell reduced average drug use from 7.22 to 4.78 prescriptions per patient.

VLASSES ET AL.[9] In a 1975 study of a Delaware SNF, Vlasses et al. showed that the following percentages of recommendations were implemented by physicians: 71% of drug-related comments (such as drug interactions), 59% of disease-management suggestions (such as duplicate medications), and 90% of administrative notes (for example, transcription errors).

TSAI ET AL.[10] This Georgia-based group

Study	**No. Patients**	**Time Period (months)**	**Location**	**Mean Prescription Reduction/Patient**
Cheung and Kayne[3]	517	11	California	1.2
Rawlings and Frisk[4]	260	54	Idaho	1.6
Hood et al.[6]	40	2	Florida	0.9
Martilla[c]	20	?	Minnesota	1.6
Lofholm	55	13	California	2.2
Cooper and Bagwell[8]	142	12	Georgia	2.44
Ellenor and Frisk[5]	475	24	Idaho	0.9
Underwood and Underwood[d]	160	?	Arkansas	1.7
Young, et al.[16]	25	1	Washington	1.8
Strandberg et al.[15]	?	96	Idaho	2.7
Wilcher and Cooper[11]	143	33	Georgia	2.4
Chrymko and Conrad[19]	21	2	New York	2.0
Thompson et al.[18]	67	24	California	2.2
Cooper[20]	77	14	Georgia	3.8
Cooper and Francisco[22]	208	30	Georgia	2.7
Average of all studies				2.00

[a] McGhan et al. applied a meta-analysis to these 15 studies. Meta-analysis is a quantitative method of combining the results of independent research findings. A fail-safe *N* is calculated to assess how many studies with no treatment effect would be necessary to cancel the accumulated effect of the reported literature. Using the technique of sensitivity analysis based on the standard deviation in number of drugs per patient, it was found that between 20 to 144 studies, each with 150 patients in each group, with no treatment effect would be needed to reduce these 15 studies to unimportant levels of effect. Based on this review, the authors concluded that pharmacist drug-regimen reviews have demonstrated a significant impact that could not be easily refuted by additional studies with less positive results.

[b] It is important to note that none of these reductions in drug use is possible without a physician's concurrence. The pharmacist is not empowered to discontinue drug therapy. In all cases, the pharmacist must convince a physician that reduced, changed, or discontinued drug therapy is in the best interest of the patient.

[c] See text footnote a.

[d] See text footnote d.

Table 1. Summary of Studies of Pharmacists' Effects on Prescription Drug Use as a Result of Drug-Regimen Review[a, b]

	Medication Orders		
Drug Class	**No. Before**	**No. After**	**% Reduction**
Antianxiety/antidepressant	160	80	50
Antipsychotic	234	193	18
Sedative/hypnotic	85	36	58
Miscellaneous	17	4	65

Table 2. Effect of Pharmacists' Recommendations on Psychoactive Drug Use in a 1974 Idaho Study[5]

Variable	Control Group	Pharmacist Group
Average prescriptions per patient	7.1	5.7
Discharged to lower level of care	2	8
Hospitalizations necessary	8	2
Patient deaths	10	3

Table 3. Effects of Pharmacists Providing Therapeutic Management in a 1981 California Pilot Project[18]

Time (months)	Pharmacist Review?	No. Medications/Patients		
		Scheduled	Nonscheduled	Total
0	No	4.95	1.52	6.47
2	Yes	3.67	0.81	4.48
14	No	4.38	1.81	6.19

Table 4. Effects of Phurmacist Reviews on Prescribing Patterns[19]

Time (months)	Pharmacist Review?	No. Medications/Patient		
		Scheduled	P.R.N.	Total
0	No	4.8	4.1	8.9
3	Yes	3.2	1.6	4.8
8	No	4.8	4.8	9.6
11	Yes	[illegible]	1.6	4.1

Table 5. Effects of Cessation of Pharmacist Reviews on Drug Use[20]

Study	No. Minutes Spent by Pharmacist Per Patient Per Month
Thompson and Floyd[14]	30.0
Thompson et al.[18]	37.2
Young et al.[16]	38.4
Rawlings and Frisk[4]	25.0
Cheung and Kayne[3]	19.7
Average of studies	30.06

Table 6. Time Spent by Pharmacists in Drug-Regimen Review

monitored hematopoietic and vitamin therapy in a 116-bed nursing home in 1976. Of 107 recommendations to physicians, 91 were accepted.

WILCHER AND COOPER.[11] In another 1976 Georgia study, Wilcher and Cooper monitored the use of anti-inflammatory and analgesic drugs in 143 patients for 33 months. Average drug use was reduced from 7.2 to 4.8 orders per patient, and the use of codeine was reduced in favor of acetaminophen.

McGHAN ET AL.[12] From 24,770 Medicaid recipients in Minnesota nursing homes, the records of 353 were randomly selected for evaluation by an expert panel using explicit drug-use criteria. The researchers found that the need for drug-regimen review was just as great in ICF patients as in SNF patients and that the frequency of reviews should be at least every 45 days.

UNDERWOOD AND UNDERWOOD.[b] In a 1978 study of 160 residents in an Arkansas ICF for the mentally retarded, these researchers reduced the average number of prescriptions per patient from 5.6 to 3.9. The cost savings for the 160 patients were estimated at $10,080 per year for drugs and $2,880 per year for reduced nursing time.

MARTTILA AND GREEN.[13] In a study of antipsychotic and antiparkinson drug use in 30 ICF patients, these researchers studied the effects of discontinuance of the antiparkinson agent for eight weeks. Results indicated that 23 of the 30 individuals needed no antiparkinson drug, and a subsequent in-service program decreased by 33% the overall use of antiparkinson drugs in the facility.

THOMPSON AND FLOYD.[14] This study in Southern California evaluated the costs of pharmacists' drug-regimen review and the resultant savings. In 31 months of drug-regimen review in 92 patients, 56 adverse drug interactions were detected; 28 were significant but no hospitalization was needed, while three were serious enough to require hospitalization. A total of $9,000 was saved from 18 avoided hospitalizations, giving a net savings of $0.26 per day. The cost of pharmacist monitoring was $0.20 per day.

STRANDBERG ET AL.[15] In monitoring residents of three Idaho nursing homes for eight years, this group reduced prescription drug orders by 42.8%, prescription drug doses consumed by 34.6%, nonprescription drug orders by 34.4%, and the average monthly bill by

$9.03 per patient.

YOUNG ET AL.[16] This group monitored 25 randomly selected SNF residents for one month in a 1981 study in Washington. Average prescription use fell from 6.0 to 4.2 per patient, the number of doses consumed dropped 18.6%, $0.25/patient/day was saved in drug costs, and $0.15/patient/day was identified as a potential savings in nursing time.

FERGUSON ET AL.[17] This study evaluated antipsychotic-drug use in 1982 in 70 residents of a Michigan ICF for the mentally retarded over a 25-month period. Using a team approach, the researchers eliminated the use of major tranquilizers in 44 of 48 residents, and the mean daily dose in those still receiving the drugs was reduced from 424 mg to 75 mg per day.

THOMPSON ET AL.[18] As a part of the California pharmacist prescribing project conducted under California bill 717, Thompson et al. studied drug monitoring for two years, one a prestudy year and the second a test year. Pharmacists could (1) make dose adjustments, (2) discontinue drugs, and (3) order laboratory tests. Table 3 outlines the results. For 67 patients in the test year, $16,080 in drug costs, $14,400 in reduced levels of care, and $24,750 in avoided hospitalizations were saved.

CHRYMKO AND CONRAD.[19] A pharmacy resident monitored 21 patients for two months in this 1982 New York study. Table 4 outlines the drug use before, at the conclusion, and several months after the conclusion of the study. This study demonstrated the need for continuous monitoring.

COOPER.[20] Another study indicating the need for continuous monitoring was this 1983 Georgia study of pharmacists' reviews in a 77-bed SNF. For four years, patients were monitored except for a three-month period and an eight-month period. Table 5 shows the increase in drug use during each period when pharmacist monitoring lapsed.

FUMIO.[21] This Canadian study recorded the results of pharmacist recommendations over a five-year period in a 400-bed ICF for the mentally retarded; a total of 680 residents were included in the study. Physicians agreed with pharmacists' recommendations more than 90% of the time for discontinuing drugs, reducing doses, changing medications, and modifying dosage increments.

COOPER AND FRANCISCO.[22] Overall drug use and antipsychotic-agent use fell in this 2.5-year study of 204 SNF patients in Georgia. The mean number of drugs per patients was reduced from 7.2 to 4.5 overall and from 1.6 to 1.1 for psychotropic drugs.

WITTE.[23] In an Illinois study of 23 SNF patients, Witte used explicit criteria for the use of digoxin. A total of 27 recommendations were made about drug interactions, potassium imbalance, and dosage; 20 were adopted by the attending physicians.

Savings from reduced drug use	$ 81,566,000
Savings from averted hospitalizations	224,000,000
Gross savings	305,566,000
Cost of pharmacist reviews	85,270,000
Net savings	**220,296,000**

Table 7. National Savings Estimated from Pharmacists' Drug-Regimen Reviews in Long Term Care

Identifying Potential Savings

From these studies, as summarized in Table 1, it appears that about two prescriptions per patient per month could be saved as a result of pharmacist monitoring of resident's drug regimens. This assumes that all drug orders are refilled each and every month, a spurious assumption. If one were to include only routine drugs in evaluating these savings, savings from reduced drug use can be more accurately estimated.

In the Cheung and Kayne study,[3] 304 drug orders were discontinued as a result of drug-regimen review, 182 (60%) of them for as-needed drugs. In the Cooper study,[20] 2.5 of the 4.1 reduced orders were for p.r.n. medications, fully 61%. The Cooper and Bagwell study[8] showed a reduction of 2.44 orders per patient, and 1.8 of these, or 74%, were for as-needed agents. These studies indicate that nearly two thirds of drug use (65%) reduced by pharmacist activity is for p.r.n. drugs. Only about 0.7 drugs per patient (35% of 2 drugs per patient) are routinely scheduled medications.

SAVINGS FROM REDUCED DRUG USE. At the time this analysis was conducted, the most recent reliable data were for the 1981 Medicaid/Medicare year and 1983 prescription prices. Use of these data underreports current potential savings. In 1981, Medicare and Medicaid paid for 10.7 million months of care in SNFs and ICFs.[c] For each of these months, Medicare and Medicaid did not have to pay for

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0.7 refills on routine drug orders, or 7.49 million prescriptions. The average prescription price in 1983 was $10.89, according to the *Lilly Digest*. The potential savings are thus $81,566,000 annually.

SAVINGS FROM AVERTED HOSPITALIZATIONS. Three studies reported the incidence of hospitalizations avoided by performance of drug reviews by pharmacists: Cheung and Kayne,[3] who found 70 hospitalizations avoided in 300 residents; Thompson and Floyd[14] whose data showed that 18 hospitalizations were avoided in 92 patients; and Thompson et al.,[18] who found six hospitalizations avoided in 67 patients. This amounts to ratio of hospitalizations per 1,000 patient-months of 19.44, 6.31 and 7.46 respectively. These ratios are somewhat consistent with Irvine et al.'s data [showing] which amounted to an overall ration for all hospitalizations of 34.82 per 1,000 patient-months.[25]

The Thompson et al. study[18] is the most reliable estimate of the number of averted hospitalizations since it reports actual hospitalizations during a control period compared with averted hospitalizations during a test period. The other two studies[3,14] used expert opinion of whether a patient would be hospitalized.

Thus, 7.46 hospitalizations per 1,000 patient-months multiplied by the number of Medicare and Medicaid months of patient care in 1981 (10.7 million) equals 79,822 averted hospitalizations. For the year ending March 1984, the cost per hospital admission was $2,797.39. As reported by the American Hospital Association giving a calculated savings of $224 million that could be attributed to pharmacist reviews of nursing home residents' drug regimens.

SAVINGS FROM REDUCED DRUG-ADMINISTRATION TIME. Three studies calculated the percentage of doses that were no longer administered as a result of drug orders discontinued after pharmacist recommendations: Strandberg et al.[15] found 34.5%; Cheung and Kayne[3] found 19.0%; and Young et al.[16] found 18.6%. The average of these three values is 24, and the average number of doses administered per patient per day in nursing homes is estimated at 10.7.[c]

If each of these doses takes 1.91 minutes to administer, as reported by Farner and Hicks[26] for a 24-hour unit dose system, the total nursing time spent per patient per day is 20.43 minutes. If the number of doses were reduced by 24%, time would be reduced by 4.9 minutes per patient per day.

In terms of dollars, this would represent about $154 million in reduced nursing time.[d] However, in most institutions, the freed time would be spent on other activities, leading hopefully to an increased quality of care.

Cost of Pharmacist Reviews

A number of studies have attempted to estimate the amount of pharmacist time spent conducting drug-regimen reviews (Table 6). Averaging the five studies listed in Table 6 shows that, to achieve the reduced drug use, hospitalization rate, and nursing time, the pharmacist spends approximately 30 minutes per patient per month reviewing records and advocating change. The cost of this time is estimated to be $85,270,000, based on 10.7 million patient-months recorded in 1981 and the pharmacist's average wage in 1983 ($15.94/hour). The cost of travel is ignored.

If in-depth drug-regimen reviews were conducted for all Medicare and Medicaid patients in SNFs and ICFs, a potential savings of $220 million can be realized (Table 7). These savings are exclusive of nearly five minutes per patient per day of additional nursing time that can be devoted to enhanced resident care.

Conclusion

In the late 1960s and early 1970s considerable public outcry about "over-drugging" and "medication errors" in nursing homes led to the 1974 federal government regulations mandating pharmacists' monthly review of SNF patients' drug regimens. The studies quoted in this paper provide convincing evidence that pharmacists have responded in a very positive way to this challenge and have ameliorated many drug therapy problems across the country. The added recognition afforded pharmacists in the latest regulation extending the requirement to ICF's is a well-earned and well-deserved recognition of consultant pharmacists' achievements.

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[a] Marttila J. Unpublished study; Pharmaceutical Consultant Services, Inc., St. Paul, Minnesota.

[b] Underwood T, Underwood F. Unpublished study; University of Arkansas College of Pharmacy, Little Rock.

[c] The 10.7 million months of SNF and ICF care under Medicare and Medicaid was arrived at by adding the number of days of care paid under Medicaid for SNF care (120,854,000) and ICF care (190,540,000) in 1981 to the days of care paid under Medicare for SNF care (8,600,000) in 1982 and dividing by 30. The Medicaid data were computed by La Jolla Management Corporation under HCFA contract 500-81-0040 in December 1983, and the Medicare data are available from the HCFA Office of Research and Demonstrations.

[d] Cost of saved nursing time was calculated as follows: 4.9 minutes/patient/day times the number of Medicaid and Medicare days of care in 1981 (320 million) times the average LPN salary in 1983 ($5.89/hour). The LPN salary was based on 1978 data from the Bureau of Labor Statistics (Bulletin 2069) increased by the change in the cost of living.

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COMMENTARY

A Job Well Done

In 1978[1] and again in 1982[2] I authored papers on the cost-benefit of pharmacist-conducted drug regimen reviews. The first of these was based on six studies and estimated the Medicare and Medicaid cost saving resulting from decreased drug utilization to be between $3.2 and 37.2 million exclusive of the cost of these reviews. This paper made several references to reduced hospital costs but did not estimate a nationwide savings.

The second paper in 1982 was based on 14 studies and estimated the Medicare and Medicaid cost saving to be approximately $25 million for skilled-nursing facilities (SNFs) and $38.4 million for intermediate-care facilities (ICFs). As with the earlier paper the 1982 publication did not estimate national savings from averted hospitalization but quoted studies that estimated these savings on a local basis.

The cost-benefit paper published in this issue[3] is based on at least 23 studies. It estimates for both SNFs and ICFs that reduction in *routine* drug utilization alone saves Medicare and especially Medicaid approximately $81.6 million. Previous cost-benefit papers estimated savings for both routine and p.r.n. drugs, but, because p.r.n. drugs are not likely to be refilled, this analysis did not include them.

This paper also points out that pharmacists have attained these savings by making recommendations to physicians. Since the physician has prescribing authority, pharmacists must first obtain their approval before these savings can be realized. Another important observation of this latest analysis is the revelation by Jim Cooper that the withdrawal of pharmacist-conducted reviews results in a rise in drug use that does not fall again until the pharmacist reinstitutes drug-regimen reviews. Thus, the positive effects pharmacists have on drug utilization is ongoing and not just a matter of "cleaning up the p.r.n.'s."

Another significant event that has occurred since the 1982 paper is Bill McGhan's meta-analysis of 15 studies of drug-regimen reviews demonstrating that these studies—conducted by independent researchers using different methodologies in different parts of the country—are a reasonably valid picture of what is taking place in the universe of facilities where reviews are conducted by pharmacists.

For the first time my paper attempts a nationwide estimate of the cost savings resulting from averted hospitalizations. It is estimated at $224 million. This estimate has been made possible primarily through the work of Thompson, McGhan and Ruffalo, who used a treatment and control group to show there was a statistical difference in rates of hospitalizations for patients with and without pharmacist-conducted drug-regimen reviews.

Also, a first for this paper is an estimate of nursing time saved as a result of drug-regimen reviews. Since drug orders are discontinued, the number of doses that must be administered are reduced. Thus, nursing time devoted to drug administration is reduced. This cost saving is estimated at $154 million nationwide. But the real significance of this saving is in the nearly five minutes for patient per day that it frees nurses to do other patient-care tasks. The Institution of Medicine (IOM) recent report on Improving the Quality of Care in Nursing Homes[4] emphasizes the need for increased nursing time and for improving quality care and quality of life for nursing home residents. Five more minutes of nursing time per patient per day can go a long way toward making a difference between implementing a bladder-training program or inserting an indwelling urinary catheter with its attendent risk of infection. It can make a lot of difference between supervising an aide to provide eating assistance as opposed to a nasogastric tube. It can go a long way toward encouraging a depressed patient to get out of bed and eat a meal in the dining hall where they could make a friend. In short it could help make the differences that could enhance a patient's quality of life.

Increased nursing time is only one way drug reviews can improve the quality of care and the quality of life. What is it worth to be free of a morning hangover caused by an unnecessary hypnotic? What is it worth to be free of exhaustion caused by unnecessary major tranquilizers? What is it worth to be able to walk to the bathroom without fear of falling—without fear of breaking a hip? Should urinary retention and constipation be treated with humiliating catheters and enemas, or should an unnecessary anticholinergic be discontinued? It is better to treat contractures and bedsores than it is to analyze the patient's drug regimen to see if a drug is causing him to be bedfast? Why don't we ask some questions? Why don't we try a drug holiday? Why don't we try discontinuing the drug to see how the patient responds? These questions don't presume the patient is beyond help! They presume the long term care patient should receive the same attention the rest of us do! These are questions long term care pharmacists are asking! Questions like these save taxpayers' dollars and enhance patient quality of life!

To all the pharmacists who ask these questions and pursue these answers—well done—well done for cost savings,well done for quality of care,well done for quality of life. But keep it up. The greatest challenge is yet to come.

Samuel W. Kidder, Pharm.D., MPH

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Item 20

Geriatric Pharmacy Curriculum in U.S. Pharmacy Schools, 1985-86

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ABSTRACT. A survey of all 72 U.S. accredited pharmacy schools revealed that at 53 schools, students are exposed to 5 to 15 hours of geriatric content in required courses in pharmacology or clinical pharmacy. Pharmacy courses focused primarily on geriatrics are required at only 9 schools. It is possible to graduate from 19 of the schools with no exposure to geriatrics. Characteristics of courses with geriatric content, the role of gerontology education programs, and recommendations for designing geriatric pharmacy coursework and clinical experiences are presented.

Currently the elderly consume over 25% of all prescription and nonprescription medications and by the turn of the century, the elderly are expected to consume well over 30% of all medications (Butler, 1980). Many pharmacists play vital roles in geriatric health care by contributing to drug therapies that respond to the unique pharmacological requirements and social and psychological characteristics of the elderly. However, pharmacists' abilities to make such contributions are dependent upon their knowledge and skills in geriatric pharmacy.

In fact, inadequate knowledge and skills in geriatrics has been identified as a significant problem by pharmacists. In one study, over 80% of the 280 pharmacists surveyed assessed themselves as not prepared or inadequately prepared for geriatric pharmacy by

their formal education (Pratt, Simonson & Lloyd, 1983). In a later survey of over 700 practicing pharmacists in Oregon, lack of knowledge in geriatrics was identified as a significant problem by pharmacists (Vorce-West, Simonson, Pratt & Ried, 1985). The majority of respondents noted that they had received less than five hours of training in geriatrics while in pharmacy school. The pharmacists in these two studies averaged 40 years of age and their formal education was completed over 16 years ago. How available is geriatric education for pharmacists now?

The present survey assessed the number and characteristics of geriatric pharmacy courses available in accredited U.S. pharmacy schools during the academic year 1985-86. All 72 of the accredited pharmacy schools in the United States responded, so that the results provide a comprehensive picture of current geriatric pharmacy curriculums.

METHOD

Survey Instrument

The survey instrument assessed the number and the characteristics of pharmacy courses with geriatric content currently offered or being developed at each school. Specifically, respondents indicated: (1) the number of courses currently offered in which 50% or more of the content was geriatrics (described hereafter as primary content courses); (2) the number of courses currently offered in which 1% to 49% of the content was geriatrics (described hereafter as partial content courses); (3) the number of primary and partial geriatric courses being developed.

Respondents also identified course titles and answered the following questions about each course: Is the course required of some or all pharmacy students? How many credits is the course and what percentage of the course is devoted to geriatrics? Does the course have a clinical component (patient contact) and if so, what percentage of the course is clinical? Is the course open to students other than pharmacy students?

Descriptive information was gathered, including: the presence and the degree of involvement, if any, that the pharmacy school had with any gerontology program at the institution; the number of pharmacy faculty with a primary interest in geriatrics; and any grants that had been received within the last five years to develop geriatric pharmacy curriculum.

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Method and Sample

A survey was sent to the Deans of each of the 72 U.S. pharmacy schools accredited by the American Association of Colleges of Pharmacy. Each survey was accompanied by a personalized letter to the Dean explaining the purpose of the survey and requesting its completion by the Dean or appropriate faculty person. Several weeks after the initial mailing of the surveys, a follow-up letter was sent to each nonresponding school. If schools did not respond to this second letter, a third and final letter was sent to a specific faculty person or to the chair of the Department of Pharmacy Practice. Using this procedure, all 72 U.S. pharmacy schools completed the survey.

The number and percentage of schools offering courses with primary and partial content in geriatrics was calculated. In addition the number and percentage of required courses and courses with a clinical component were calculated. Chi-square analysis was utilized to examine for possible relationships between selected course characteristics.

RESULTS

A total of 339 courses were identified as containing some geriatric content. The number of schools offering geriatric coursework is shown on Table 1. While 39 schools (54%) offered both primary and partial content courses, 6 schools (8%) offered no geriatric coursework.

Of the 44 schools with primary content courses, 17 (38%) offered one course, 15 (34%) offered two courses, 8 (18%) offered three courses, and 4 (9%) schools offered four or five courses. Of the 61 schools offering partial content courses, either alone or in combination with primary content courses, 9 schools (15%) offered one course, 30 schools (49%) offered two to five courses, 20 schools (33%) offered six to ten courses and two schools (3%) offered 18 courses in which geriatrics was addressed in some way.

Only 9 schools (13%) required pharmacy students to take a primary geriatric content course while 53 schools (74%) required students to take at least one partial content course. All of the schools that required primary geriatric content courses also required partial content courses, thus 19 schools (26%) had no required coursework in geriatrics.

TABLE 1

NUMBER AND PERCENTAGE OF US PHARMACY SCHOOLS OFFERING GERIATRIC COURSEWORK IN 1985-86 (N = 72)

	Number (Percentage)
TYPE OF GERIATRIC COURSEWORK	
No geriatric coursework	6 (8%)
Only primary* coursework	5 (7%)
Only partial** coursework	22 (31%)
Both primary and partial coursework	39 (54%)
REQUIRED GERIATRIC COURSEWORK	
Schools requiring some primary coursework for all students	9 (13%)
Schools requiring some partial coursework of all students	53 (74%)
Schools not requiring any geriatric coursework	19 (26%)

* primary coursework = 50% or more of content is geriatrics

** partial coursework = less than 50% of content is geriatrics

Course Characteristics

The characteristics of the 339 geriatric content courses are shown in Table 2. Most (74%) of the 98 primary content courses were elective and 37% included a clinical component. Over 70% of these clinical experiences described were in nursing home settings.

In the 241 partial content courses, the average amount of geriatric

TABLE 2

NUMBER AND PERCENTAGE OF PRIMARY AND PARTIAL GERIATRIC PHARMACY COURSES BY COURSE CHARACTERISTICS

	PRIMARY GERIATRIC CONTENT COURSES	PARTIAL GERIATRIC CONTENT COURSES
Total number of courses with geriatric content	98	241
Mean percentage of geriatric content in courses	94.3%	15.8%
Courses required of		
-all students	10 (10%)	48 (20%)
-some students	15 (15%)	127 (53%)
-not required of any students	73 (74%)	66 (27%)
Presence of clinical component in course	36 (36.8%)	72 (30.1%)
Mean percentage of clinical experience in courses with clinical component	67.6%	31.2%
Open to non-pharmacy students	21 (21%)	15 (6%)

content was 15.8%, or the equivalent of four to five hours in a 30 contact hour course. Approximately half (53%) of the partial content courses were required of some pharmacy students and 20% were required of all pharmacy students. A clinical component was included in 30% of the partial content courses.

Comparing primary content to partial content courses, it was found that partial content courses were significantly more likely to be required for some ($X^2 = 4.79$, df = 1, $p < .01$) or all pharmacy students ($X^2 = 39.07$, df = 1, $p < .01$). There was no significant association between amount of geriatric content (primary or partial) and the presence of a clinical component in a course ($X^2 = 1.01$, df = 1, ns).

Nonpharmacy Students in Courses

A total of 36 (11%) of the geriatrics courses were open to nonpharmacy students (Table 2). Primary content courses were significantly more likely to be open to nonpharmacy students than were partial content courses ($X^2 = 15.68$, df = 1, $p < .01$).

The 21 primary content courses that were open to nonpharmacy students fell into two major categories. The first category consisted of 14 didactic courses on geriatric drug therapy or similar topics. The second category included seven clinical seminars or interdisciplinary "team building" courses, focused most often on geriatric treatment in nursing homes. Only 15 (6%) of the partial content courses were open to nonpharmacy students. Most of these courses were advanced pharmacy courses in clinical pharmacy. Three were elective survey type courses such as "Medicine in Society."

Health sciences students in medicine and nursing were the students who were most often eligible for enrollment in geriatric pharmacy courses. Only seven courses were open to any interested student including those in social work, counseling, psychology and gerontology. Only three schools identified courses with geriatric content which were designed specifically for nonpharmacy students.

Courses Being Developed

Seventeen schools (24%) stated plans to develop one or more primary content courses within the next two years. Eight schools (11%) planned to develop one or more partial content courses. Schools which currently offered only one or two partial content courses were the most likely to be developing new coursework. Over 76% of all schools were not developing any new coursework in geriatrics, including five of the six schools with no current coursework in geriatrics.

Factors Associated with Geriatric Curriculum

Most schools of pharmacy offered some coursework in geriatrics. Schools with graduate programs in pharmacy had the most extensive curriculums in geriatrics, and most offered at least one partial and one primary content course. All six of the schools with no coursework in geriatrics had only baccalaureate programs.

Compared to the pharmacy schools with no gerontology program at their institution, schools at institutions with such a program were significantly more likely to offer both primary and partial content courses in geriatrics ($X^2 = 5.49$, $df = 1$, $p < .05$). Further for the 48 schools with gerontology programs at their institutions, the degree of involvement with these programs was associated with the amount of geriatric pharmacy coursework that was offered ($X^2 = 11.62$, $df = 1$, $p < .01$). Specifically, 23 (74%) of the 31 pharmacy schools offering both primary and partial content courses in geriatrics reported moderate to great involvement with a gerontology program. Only four (24%) of the 17 schools with no geriatrics courses or only partial content courses reported moderate or great involvement with a gerontology program.

Twelve (17%) of the schools reported receiving outside funds in the last five years to develop their geriatrics curriculum. All 12 of these schools offered both primary and partial content courses in geriatrics. Two-thirds of the awards were from government sources and one-third were from private sources. Most of the awards were under $25,000.

The presence of faculty with a primary interest in geriatrics was associated with the availability of coursework in geriatrics. Thirty-seven (95%) of the 39 schools with both primary and partial geriatrics content courses reported having at least one faculty with a primary interest in geriatrics. Similarly, four of the five schools with primary only courses reported having such faculty. Only six of the 22 schools with partial only content and one of the six schools with no geriatric coursework reported having faculty with primary interest in geriatrics.

DISCUSSION AND RECOMMENDATIONS

Two basic types of geriatrics courses are currently available to U.S. pharmacy students. The most common type of course is one that is required of students but contains only a small percentage (averaging about 16%) of content on geriatrics. This type of course is best typified as a required didactic pharmacy practice or pharmacology courses that includes one to five lectures on geriatrics. The second general type of geriatrics courses is an elective course which focuses entirely on geriatrics. While such courses offer an excellent opportunity to learn about geriatrics, most are elective and most students are not exposed to them.

Not all schools with geriatric content courses require students to

take any of this coursework. When it is required, exposure to geriatrics is most often limited to four to five lectures offered in one or two required courses in pharmacology or clinical pharmacy. It is possible to graduate from over one-quarter of all pharmacy schools with *no* required exposure to geriatrics.

At the time of the survey most schools indicated that they were not developing any new coursework in geriatrics. Certainly many of the schools had geriatric course content which they perceived to be sufficient. However, it is disturbing that only 10 of the 22 schools currently offering only partial content courses are developing more geriatric coursework. It is even more disturbing that only one of the six schools with no geriatric coursework is currently developing such courses.

Recommendations

Several recommendations for geriatric education in pharmacy schools can be made. First, given the elderly's extensive use of pharmaceutical services, it is essential that *all* pharmacy schools offer *required* coursework in geriatrics. Recent studies have suggested the content areas that are critical to geriatric pharmacy (Pratt & Simonson, 1982; USDHEW, 1979). At a minimum, this coursework should provide students with a basic knowledge of the following areas: (1) age-related changes in physiology that affect the absorption, distribution, metabolism, and excretion of medications; (2) the increased incidence and nature of adverse drug reactions and drug interactions in the elderly; (3) the common health disorders affecting the elderly and the drug treatments for these disorders; and (4) the factors, including sensory changes, economics, and other psychosocial factors that influence patient communication, education and compliance. A minimum of 30 total hours of classroom instruction seems necessary to introduce students to these basic concepts.

Second, because partial content coursework appears to be the most likely vehicle through which to offer pharmacy content, it is essential that the the coverage of geriatric content be carefully coordinated between courses. Such coordination will insure that all important aspects of geriatrics are covered in courses. The obvious advantage of coordinating the content presented in courses is that the same "introduction to gerontology and geriatrics" lectures will not be repeated in several courses. When geriatric content is coordinated across several courses, students can be exposed to the wide range of physiological, social, psychological and practice issues that are the heart of a basic understanding of geriatric pharmacy.

Third, because a large number of elderly patients are found in almost all pharmacy practice environments, most clinical experiences will include exposure to some older patients. A basic understanding of geriatric issues in pharmacy should proceed these clinical experiences which are required of all pharmacy students.

Fourth, in both classes and clinical experiences, students should be exposed to a variety of elderly patients and geriatric pharmacy issues. Currently the vast majority of clinical experiences which are specifically directed at geriatric pharmacy are in nursing home settings. Research with student nurses has indicated that clinical experiences in nursing homes many result in the development of more negative attitudes toward the elderly particularly if these experiences occur early in professional training and are not proceeded by adequate classroom preparation (Cook & Pieper, 1985). While nursing home experiences are valuable to pharmacy students, all future pharmacists should be exposed to the full range of geriatric patients during their academic preparation.

Fifth, pharmacy schools, particularly those with graduate programs, should consider developing advanced coursework and clinical experiences in geriatrics. Such courses would enable students to expand their background in geriatrics or to specialize in geriatrics. This coursework would very likely be elective and could be offered to health sciences and gerontology students who have a specific interest in geriatric pharmacy. The nursing home "team building" seminars described by some of the pharmacy schools are examples of efforts to acquaint pharmacy and other students with the complexities and rewards of interdisciplinary practice in geriatrics. Some schools may also want to offer courses specifically for non-pharmacy students to acquaint them with the essentials of geriatric pharmacy (Simonson & Pratt, 1983). Whatever its exact nature, advanced coursework in geriatric pharmacy can create a cadre of pharmacists and other professionals with the expertise needed to serve as leaders in geriatric pharmacy research and clinical practice.

Sixth, at institutions where gerontology education programs exist, interactions between these programs and pharmacy schools should be actively pursued. This survey demonstrated that such interactions were associated with more extensive geriatric pharmacy coursework. The exchange of faculty lectures is an example of a simple but potentially valuable interaction. Gerontology faculty can offer guest lectures in demographics, sensory changes, communication, social and psychological aspects of aging and other topics to pharmacy classes. Pharmacy faculty can introduce gerontology students to the issues of medication use, age-related physiological changes that affect medications and other topics. Thus both gerontology and pharmacy curriculums may be enriched.

Finally, it is recommended that schools utilize their available resources to develop a basic core of geriatric content courses. This survey demonstrated that the presence of interested pharmacy faculty and liaisons with gerontology programs were more critical to the offering of geriatrics coursework than the availability of outside grants to develop such coursework. While grants can be invaluable to develop extensive curriculums, schools without such grants can still pursue the development of geriatric coursework utilizing interested faculty and, if present, the expertise of gerontology programs. Other resources for curriculum development include recent articles and comprehensive guides on geriatric pharmacy curriculums (Ameer, 1985; Parham & Teitelman, 1984; Parham, Teitelman & Yancey,1981; Pratt & Simonson, 1982; Simonson & Pratt, 1983; Simonson, 1984).

SUMMARY

Pharmacists may play vital and productive roles in geriatric health care. Their ability to do so, however, is dependent upon their access to adequate professional training in geriatrics. This nationwide survey indicates that most pharmacy schools require only 5 to 15 hours of exposure to geriatrics presented as a small part of the content of required courses in pharmacology or pharmacy practice. Further, it is possible to graduate from over one-quarter of U.S. pharmacy schools with no required exposure to geriatrics. In particular, schools with baccalaureate programs in pharmacy are likely to offer very limited or no geriatrics content. Yet these schools are responsible for training many of the "frontline" pharmacists who regularly serve the elderly in community pharmacies and other clinical settings, including hospitals, nursing homes, and home health care programs.

Pharmacy schools should assess their current offerings in geriatrics and ensure that all students are exposed through required courses and clinical experiences to the fundamentals of geriatric pharmacy practice with a wide range of older patients. Gerontology programs should work with pharmacy educators to support the development of geriatric pharmacy education. This education is fundamental to high quality pharmaceutical services for today's and tomorrow's elderly.

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Study, action urged to cut drug reactions in elderly

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AMN CORRESPONDENT

An influential senator says the elderly suffer too high an incidence of adverse drug reactions and he urged better education for health professionals, increased testing, and more informative labeling to curb the problem.

Sen. John Melcher (D, Mont.), chairman of the Senate Special Committee on Aging, convened a Senate hearing to explore ways to reduce occurences of adverse drug reactions among the elderly. Federal Food and Drug Administration (FDA) numbers from 1986 show that people 60 and older — representing about 17% of the general population — account for more than half of the 1,347 deaths from adverse drug reactions and 39% of the 4,481 hospitalizations, he said.

"Moreover, these total figures may very well represent the tip of the iceberg, since most reporting of such reactions to the FDA is voluntary," Melcher said.

"Adverse drug reactions are costly not only in terms of human suffering, but also in unnecessary and significant expenditures from the Medicare program, the Medicaid program, and from the pocket of older Americans."

He pointed out that the Medicare program currently reimburses elderly patients for inpatient prescription drugs. "But the expected enactment of the new catastrophic health care drug benefit can only increase the amount of unnecessary program expenditures on inappropriate drug therapy and the associated health care required to care for victims of adverse drug reactions," he said.

JAMES SAMMONS, MD, submitted a letter to Melcher and the committee on behalf of the American Medical Assn. noting that the AMA historically has played "a key role in providing physicians and the public with unbiased information on adverse drug reactions." He cited several positions and projects of the AMA, including the Prescription Abuse Data Synthesis (PADS) model, that help accomplish that goal. PADS is an AMA project used by physicians in the fight to diminish overprescribing and adverse drug reactions.

One reason for the problem, Melcher said, is the revolutionary advances in the use of pharmaceuticals in recent years. Since 1976, for example, the FDA has approved more than 1,000 new drugs, and more than 10,000 drugs currently are available for health care providers to prescribe, he said.

Although older Americans represent only 12% of the population, Melcher said, they consume approximately one-third of all prescription drugs. This means that older people stand to benefit most from advances in drug therapy but also are far more vulnerable to adverse drug reactions and interactions.

"Surveys show that education of physicians and other health care providers on drug use, especially multiple drug use in the elderly, is not keeping pace with the rapid advances in drug therapies," Melcher said. Furthermore, he said, reports from the Dept. of Health and Human Services (HHS) and the Institute of Medicine indicate that geriatric training, including geriatric pharmacological training, are inadequate in many of the nation's medical schools.

Melcher said he thought Congress should take the following steps to help solve the problem:

- ■ Review FDA policies for approving and updating drug labels that advise physicians and other health care providers on proper drug prescription and use.

'Education of physicians on multiple drug use in the elderly is not keeping pace with the rapid advances in therapies.'

Sen. John Melcher

- ■ Encourage the FDA to publish its guidelines for clinical testing of new drugs for the elderly, which would require manufacturers to determine whether a new drug is more likely to elicit an adverse reaction from an elderly person.
- ■ Support initiatives that would encourage medical schools to place more emphasis on geriatric training and provide more information about the special pharmacological needs and vulnerability of the elderly.
- ■ Fund more studies on methods to give information to medical personnel who appear to be inappropriately or excessively prescribing medications that are known to pose particular dangers to the elderly.
- ■ Support studies on drug categories widely used by the elderly that would provide more information on potential occurednces of adverse drug reactions.

"I believe these options have the very real potential to save lives as well as to reduce prescription drug costs," Melcher said. He cited a report from the American Assn. of Retired Persons saying that elderly people spent $9 billion on prescription drugs in 1986 and that 81% of the costs came from their own money.

Jerry Avorn, MD, said some modern prescription drugs can produce therapeutic benefits that are unprecedented. "However, this same power makes them capable of producing a wide variety of adverse drug effects," he testified at the hearing.

"THE ELDERLY are particularly vulnerable to these effects because their livers and kidneys are often less able to metabolize and excrete drugs, their bodies are more sensitive to drug effects, and they are far more likely to be taking a combination of medication and have a variety of potentially complicating diseases as well," said Dr. Avorn. He is the director of the Program for the Analysis of Clinical Strategies at Harvard Medical School.

He said greater numbers of older people are taking more powerful medications under the direction of physicians who often have not received much training in the proper use of drugs for the elderly.

"To some extent, this educational void is filled by the promotional and educational activities of drug companies, but since the ultimate purpose of such communications is to persuade physicians to prescribe a particular product, these activities cannot make up for the absence of broad-based noncommercial education of physicians in this area," Dr. Avorn said.

Like Melcher, Dr. Avorn also stressed testing. "Although the FDA has been discussing the possibility of guidelines for including the elderly in premarketing testing of drugs for years no requirement has been promulgated, and there has been great variability in the eagerness with which drug companies have sought out the elderly in the investigational stages of a new drug," he said.

Dr. Avorn and colleagues studied 435 physicians measuring the effects of presenting concise, valid, scientific information in short tutorial sessions in physicians' offices aimed at encouraging appropriate prescribing practice.

"WE WERE able to reduce inappropriate prescribing by 14%, compared to physicians randomized into the control group," he said.

"We actually were able to save the state Medicaid programs in the four study states twice as much as it cost to mount the program." He said health care providers elsewhere had adopted this program with similar positive results.

Dr. Avorn and his colleagues now are developing a database containing information on all use of medication and clinical encounters of patients in Medicaid, Medicare, and Pharmacy Assistance of the Aged and Disabled program in New Jersey.

"This makes it possible to follow in great detail the rates of adverse effects associated with the use of various medications in a population which now exceeds a million patients," he said.

"Drawing together the insights of geriatric medicine, epidemiology, computer science, and health services research, we are attempting to learn how such powerful databases can be used to inform the practice of medicine, particularly in relation to the study of drug effects in the elderly."

Dr. Avorn said that HHS, through its various branches, should intensify efforts to understand the effects of widespread use of powerful new medications in an aging population "before we are obliged to learn about them the hard way."

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William Simonson, a clinical pharmacist and associate professor of pharmacy at Oregon State U., testified that the absence of sufficient labeling information presents problems for health providers and older people.

"**DETAILED** and clinically usable information is still unavailable for most drug products," he told the committee. "For example, scrutiny of the available product labeling in 1981 showed that a specific geriatric dosage was available for only 17 of the 200 most commonly prescribed medications, and a specific note on adverse reaction was provided in only 18 of the top 100. It is not much improved today."

Simonson said he thought specific geriatric labeling for all products commonly used by the elderly is both desirable and feasible. "The labeling could define a specific geriatric dosage, or it could refer to more general precautions."

He said he thought the pharmaceutical manufacturing industry has a sincere interest in finding solutions to promote safety and to improve the effectiveness of medications used by elderly people. He cited a recent report from the Pharmaceutical Manufacturers Assn. concerning the results of new research about prescription drugs for the elderly.

The report recommended, among other things, establishing centers for geriatric pharmacology and nursing home pharmacology. He said such centers would be positive steps.

"It is also my opinion that the pharmaceutical industry should provide the funds that would be required to develop these centers," he said. "This would be logical because the information gained ... would ultimately lead to more effective use of medications in the elderly while, at the same time, increasing pharmaceutical sales to this rapidly growing segment of the population."

SIMONSON SAID the FDA should require manufacturers to provide drug labeling that would include a specific statement of the likelihood of adverse drug reactions occurring in elderly patients and recommended specific geriatric dosages.

He said the FDA also should require performance of adequate geriatric studies before approval of any new drug to learn more about the effects of the drugs on elderly people. Simonson also sees the need to require post-marketing surveillance of drug effects to observe the impact on large populations of elderly consumers of medications.

"In this way, the occurrence of adverse drug reactions could be noticed as soon as possible after a drug product is marketed," he said. "The early discovery of such problems would aid in the development of appropriate interventions such as dosage alterations so that the problem could be reduced or eliminated."

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